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STUDY EV-103 COHORT L: EVALUATING PERIOPERATIVE ENFORTUMAB VEDOTIN MONOTHERAPY IN CIS-INELIGIBLE MUSCLE INVASIVE BLADDER CANCER (MIBC) (TRIAL IN PROGRESS)

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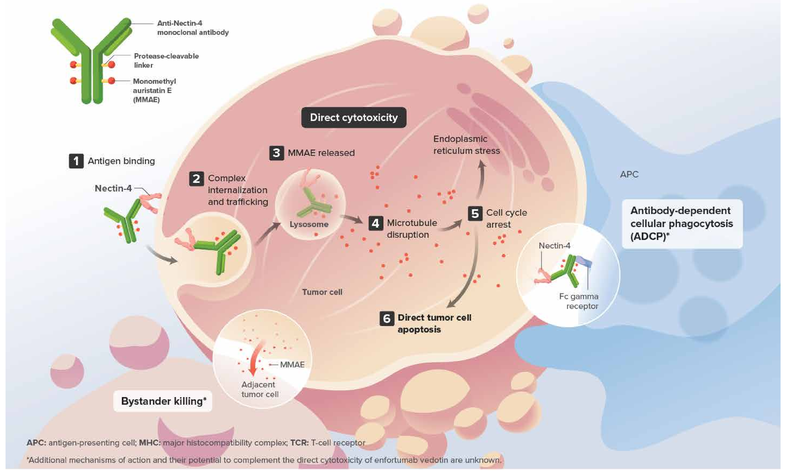
Background

- Up to 25% of all patients diagnosed with urothelial cancers present with MIBC[1]
- Neoadjuvant cisplatin-based chemotherapy followed by RC+PLND is recommended by various guidelines;[2,3] however, there is a high rate of recurrence (20%–50%) in patients who are cisplatin-ineligible and receive RC+PLND alone[4]
- Patients with residual disease after RC may be considered for adjuvant therapy[4]
- Safe and effective perioperative therapies are an unmet need for patients with MIBC who are cisplatin-ineligible
- EV is an antibody–drug conjugate directed to Nectin-4, a protein highly expressed in urothelial cancer and other solid tumors[5,6]
  - In a Phase 3 trial, EV showed improved OS versus chemotherapy and a tolerable safety profile in patients with la/mUC previously treated with chemotherapy and PD-1/L1 inhibitor[5]
  - Efficacy and safety has also been established in cisplatin-ineligible patients with previously treated la/mUC[5,7]
- EV-103 is a multicohort Phase 1b/2 study designed to evaluate EV as monotherapy or in combination in 1L or 2L la/mUC or MIBC (ClinicalTrials.gov, NCT03288545)
- Preliminary results of EV-103 Cohort H showed promising antitumor activity in patients with MIBC who are cisplatin-ineligible[8]
- Given the efficacy of EV in la/mUC and encouraging results in MIBC, EV will be evaluated in EV-103 Cohort L as perioperative therapy in patients with MIBC who are cisplatin-ineligible

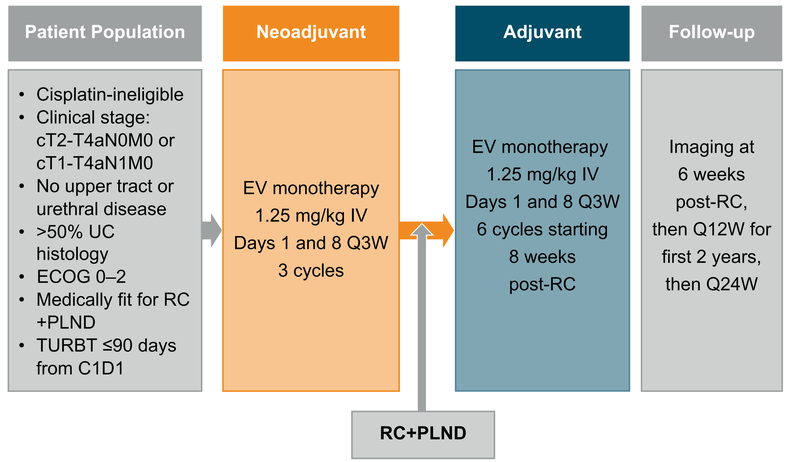
Enfortumab Vedotin Proposed Mechanism of Action



Enfortumab vedotin is an investigation agent in some settings, and its safety and efficacy have not been established.

Methods

EV-103 Cohort L: Perioperative EV in MIBC (N=50[a])



- Primary endpoint: pCR (absence of viable tumor in examined tissue from RC+PLND)
- Key secondary endpoints: EFS, pDS, DFS, OS, and safety

a Sample size is approximate and is based on the precision of estimate for pCR rate as characterized by the 95% confidence interval.

C1D1, day 1 of treatment cycle 1; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EV, enfortumab vedotin; IV, intravenous; MIBC, muscle invasive bladder cancer; OS, overall survival; pCR, pathological complete response; pDS, pathological downstaging; PLND, pelvic lymph node dissection; QXW, every X weeks; RC, radical cystectomy; TURBT, transurethral resection of a bladder tumor; UC, urothelial cancer

Cohort L Key Eligibility Criteria

- Histologically confirmed MIBC (predominant urothelial type [ie, >50%])
- ECOG performance status of ≤2
- Eligible for and agree to undergo RC+PLND
- Clinical stage of cT2-T4aN0M0 or cT1-T4aN1M0 based on pathology and imaging reviews
- Ineligible for cisplatin-based chemotherapy due to ≥1 of the following:
  - GFR 30–<60 mL/min
  - ECOG performance status of 2
  - NCI CTCAE Version 4.03 grade ≥2 hearing loss
  - NYHA Class III heart failure
- No prior systemic treatment, chemoradiation, or radiation therapy for MIBC
- May have received prior intravesical Bacillus Calmette–Guérin or intravesical chemotherapy for non-MIBC
- Available tumor samples sufficient for pathology review and biomarker analysis
- Adequate hematologic and organ function tests

Complete Objectives and Endpoints

Primary and Secondary Efficacy Objective	Primary and Secondary Efficacy Endpoints
To assess antitumor activity of perioperative EV monotherapy	**Primary endpoint:** • pCR rate[a] by central pathology review **Secondary endpoints:** • EFS[b] by BICR and by investigator • pDS rate[c] by central pathology review • DFS[d] by BICR and by investigator • OS
Secondary Safety Objective	**Safety Endpoints**
To assess safety and tolerability of EV monotherapy	• Type, incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities • Delay of RC+PLND due to treatment-related AEs
Exploratory Objectives	**Exploratory Endpoints**
To assess patient-reported experience and tolerability of treatment	Change from baseline in PRO assessment EQ-5D-5L
To assess Nectin-4 and PD-L1 expression levels	Exploratory biomarkers of clinical activity
To assess biomarkers of biological activity and disease resistance and their potential associations with clinical outcome measures	Selected plasma and serum PK parameters of EV, MMAE, and TAb
To assess PK and the incidence of ATA	Incidence of ATA to EV

a Defined as the absence of viable tumor (pT0N0) in examined tissue from RC+PLND
b Defined as the time from the start of study treatment to the first occurrence of any of the following events: radiographic disease progression precluding a curative intent surgery prior to RC+PLND, failure to undergo RC+PLND for patients with residual muscle-invasive disease and/or any radiographic disease present, gross residual disease left behind at time of RC+PLND, local or distant recurrence post-RC as assessed by CT or MRI and/or biopsy, or death from any cause
c Defined as patients with tumors ≤pT2 (includes pT0, pTis, pTa, pT1) and N0 in examined tissue from RC+PLND
d Defined as the time from post-RC baseline scan to the first occurrence of either local or distant recurrence as assessed by CT or MRI and/or biopsy or death due to any cause

Response and Safety Assessments

Responses:

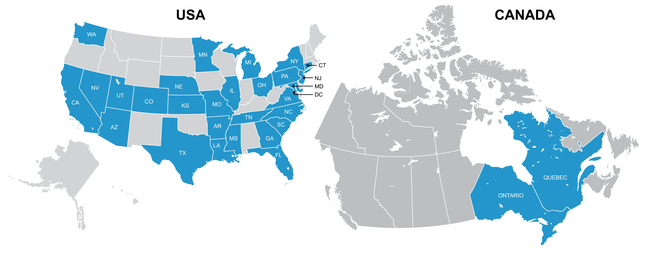
- Imaging: Screening, ≤4 weeks prior to RC, 6 weeks post-RC, Q12W until end of 2 years post-RC, then Q24W
- Centrally reviewed pathology at RC+PLND
- Survival and disease status: Patients will be contacted during long-term follow-up until death, study closure, or withdrawal, whichever occurs first

Safety and tolerability:

- Type incidence, severity, seriousness, and relatedness of AEs and laboratory abnormalities collected throughout both neoadjuvant and adjuvant treatment periods though EOT or 30 days post study intervention, whichever is later

Study Sites

- Cohort L is currently enrolling in the United States and Canada (active sites are in blue)



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Abbreviations

1L, first-line; 2L, second-line; ADCP, antibody-dependent cellular phagocytosis; AE, adverse event; APC, antigen-presenting cell; ATA, antitherapeutic antibodies; BICR, blinded independent central review; C1D1, day 1 of treatment cycle 1; cis, cisplatin; CT, computed tomography; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; EOT, end of treatment; EQ-5D-5L, EuroQoL-5 Dimensions; EV, enfortumab vedotin; GFR, Glomerular Filtration Rate; IV, intravenous; la/mUC, locally advanced/metastatic urothelial cancer; MIBC, muscle invasive bladder cancer; MHC, major histocompatibility complex; MMAE, monomethyl auristatin E; MRI, magnetic resonance imaging; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA, New York Heart Association; OS, overall survival; pCR, pathologic complete response; pDS, pathological downstaging; PD-L1, programmed death ligand 1; PK, pharmacokinetics; PLND, pelvic lymph node dissection; PRO, patient-reported outcome; QXW, every X weeks; RC; radical cystectomy; TAb, total antibody; TCR, T-cell receptor; TURBT, transurethral resection of a bladder tumor; UC, urothelial cancer