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# STUDY EV-104: PHASE 1 STUDY OF INTRAVESICAL ENFORTUMAB VEDOTIN FOR TREATMENT OF PATIENTS WITH NON-MUSCLE INVASIVE BLADDER CANCER (NMIBC) (TRIAL IN PROGRESS)

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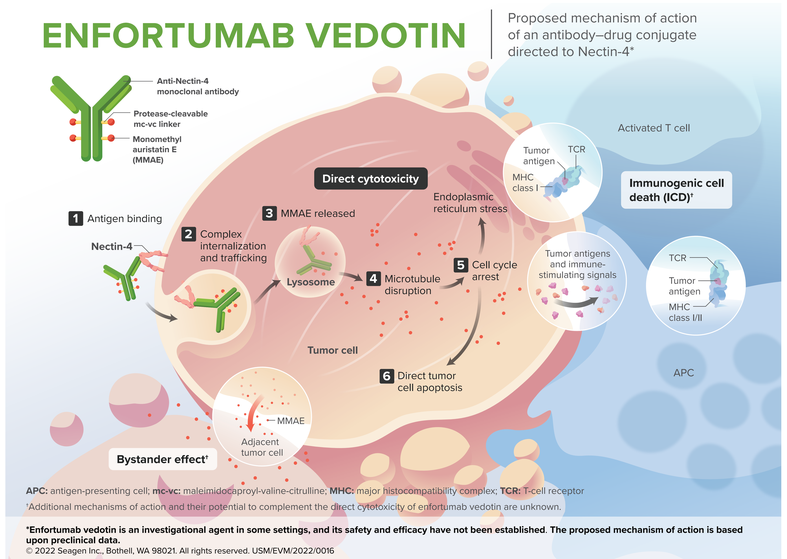
## Background

- A majority of patients with bladder cancer present with non-muscle invasive disease[1–4]
- Non-muscle invasive bladder cancer (NMIBC) with a higher risk of recurrence is typically treated with TURBT followed by intravesical BCG or chemotherapy
  - Although response rates to BCG are high, many patients recur within 1–5 years[5]
- Radical cystectomy is the standard of care for BCG-unresponsive disease[1]
  - Other options are limited to intravesical chemotherapy or PD-1 inhibitors for patients who may be reluctant to undergo surgery[6]
- Enfortumab vedotin (EV) is an antibody-drug conjugate directed to Nectin-4, which is highly expressed in all stages of bladder cancers[7]
- EV is tolerable and effective in advanced urothelial cancers
  - In a Phase 3 trial, intravenous EV monotherapy showed improved OS versus chemotherapy and a tolerable safety profile in patients with locally advanced/metastatic urothelial cancer, prior chemotherapy, and PD-1/L1 inhibitor treatment[8]
  - In a Phase 1b/2 trial, antitumor activity and a tolerable safety profile has also been established in cisplatin-ineligible patients with MIBC in the neoadjuvant setting[9]
- This study will evaluate the intravesical administration of enfortumab vedotin for patients with BCG-unresponsive high-risk NMIBC

## Enfortumab Vedotin Proposed Mechanism of Action




***Enfortumab vedotin is an investigational agent in some settings, and its safety and efficacy have not been established. The proposed mechanism of action is based upon preclinical data.**



### References

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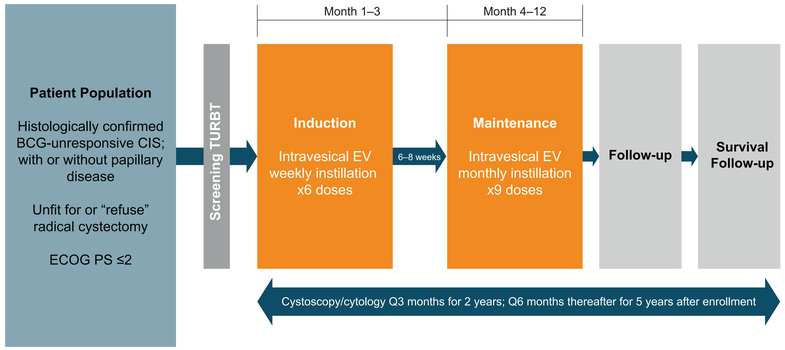
## EV-104 Study Design

**EV-104 (NCT05014139) is a Phase 1, open-label, multicenter, dose-escalation and dose-expansion study designed to evaluate the safety, tolerability, PK, and antitumor activity of intravesical enfortumab vedotin in adults with NMIBC**




- The study treatment regimen will include an induction phase where patients will receive intravesical enfortumab vedotin weekly for 6 weeks followed by monthly maintenance for a total of 9 additional enfortumab vedotin doses
- To identify the recommended dose, escalation rules will be guided by the modified toxicity probability interval (mTPI) design using a Bayesian model for "escalation", "stay", or "de-escalation" (Approximately 18 patients)
- The recommended dose or MTD will be evaluated in up to 2 dose expansion cohorts (up to approximately 40 patients)

## Eligibility

### Key Inclusion Criteria

- High-risk BCG-unresponsive disease
- Histologically confirmed, non-muscle invasive urothelial (transitional cell) carcinoma with carcinoma in situ, with or without papillary disease
- Predominant histologic component (>50%) must be urothelial (transitional cell) carcinoma
- Ineligible for or refusing a cystectomy
- ECOG PS ≤2
- Estimated life expectancy of >2 years

### Key Exclusion Criteria

- Current or prior history of muscle-invasive UC or metastatic disease
- Concomitant upper tract or urethral disease
- Any prior radiation to the bladder for UC

### Abbreviations

AE, adverse event; BCG, Bacillus Calmette-Guerin; CIS, carcinoma in situ; CR, complete response; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Performance Status; EV, enfortumab vedotin; Fc, fragment crystallizable; MIBC, muscle-invasive bladder cancer; MMAE, monomethyl auristatin E; MTD, maximum tolerated dose; mTPI, modified toxicity probability interval; NMIBC, non-muscle invasive bladder cancer; OS, overall survival; PD-1/L1, programmed cell death protein 1/programmed death –ligand 1; PFS, progression-free survival; PK, pharmacokinetics; Q, every; SAE, serious adverse event; TURBT, transurethral resection of the bladder tumor; UC, urothelial carcinoma

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## Key Study Assessments

### Safety and Tolerability

- Surveillance and recording of AEs, including SAEs, recording of concomitant medications, and measurements of protocol-specified physical examination findings and laboratory tests

### Efficacy

- Patients will be assessed by cystoscopy and urine cytology at screening, every 3 months (±2 weeks) from the first induction dose for the first 2 years, and every 6 months (±2 weeks) after this for five years
- Annual upper tract imaging as clinically indicated during treatment
- Bladder mapping biopsies by local assessment at 12 months

## Objectives and Associated Endpoints

| Primary Objective | Primary Endpoint |
|---|---|
| To evaluate the safety and tolerability of intravesical EV in patients with NMIBC | Type, incidence, severity, seriousness, and relatedness of AEs<br>Type, incidence, and severity of laboratory abnormalities |
| To identify the MTD or recommended dose of intravesical EV in patients with NMIBC | Incidence of DLTs and cumulative safety by dose level |
| **Key Secondary Objectives** | **Key Secondary Endpoints** |
| To assess the PK of intravesical EV | Estimates of selected PK parameters |
| To assess the antitumor activity of intravesical EV as measured by CR rate | CR rate at any time on study and CR rates at 3, 6, 12, 18, and 24 months |
| To assess the duration of CR, PFS, and cystectomy-free survival | Duration of CR, progression-free survival, and cystectomy-free survival |

## Summary

- EV-104 aims to:
  1) identify the maximum tolerated dose (MTD) and/or recommended dose of intravesical enfortumab vedotin (dose escalation); and
  2) evaluate safety and antitumor activity for patients at the MTD or recommended dose (dose expansion cohort(s))
- Enrollment began in January 2022 and sites are currently enrolling in the US, Canada, UK, and EU