A First-In-Human Trial of Intravesical Enfortumab Vedotin (EV), an Antibody-Drug Conjugate (ADC), in Patients with Non-Muscle Invasive Bladder Cancer (NMIBC): Interim Results of a Phase 1 Study (EV-104)

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Objectives

Investigate the use of intravesical EV in patients with NMIBC

- Evaluate the safety and tolerability of intravesical EV
- Identify the MTD or recommended dose of intravesical EV
- Assess the PK of intravesical EV
- Assess preliminary antitumor activity of intravesical EV

Summary

Preliminary data shows intravesical EV is well tolerated in patients with NMIBC

- There were no DLTs observed, SAEs, or grade ≥3 TRAEs

There is no evidence of systemic exposure with intravesical EV at 125 mg

Encouraging preliminary antitumor activity was observed

- 3 of 5 evaluable patients achieved a CR at the time of data cutoff

Dose escalation is ongoing to identify the MTD or recommended dose for dose expansion

Abbreviations

ADC, antibody-drug conjugate; BCG, Bacillus Calmette-Guerin; CIS, carcinoma in situ; CR, complete response; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Score; EV, enfortumab vedotin; Ia/mUC, locally advanced/metastatic urothelial cancer; MIBC, muscle-invasive bladder cancer; MMAE, monomethylauristatin E; MTD, maximum tolerated dose; NMIBC, non-muscle invasive bladder cancer; ORR, objective response rate; OS, overall survival; PD, persistent disease; PK, pharmacokinetics; Q, every; SAE, serious adverse event; SOC, standard of care; TRAE, treatment-related adverse event; TURBT, transurethral resection of the bladder tumor; yrs, years

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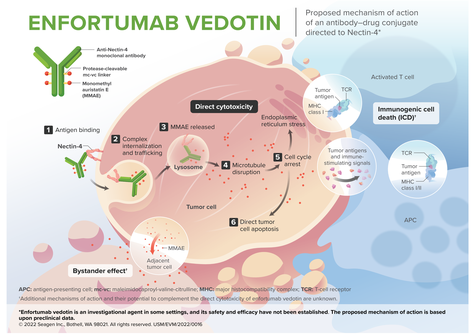
Background

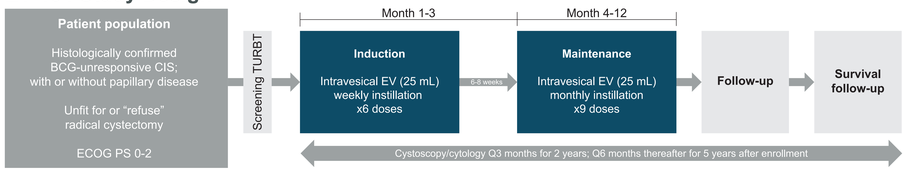
- Most patients with bladder cancer present with non-muscle invasive disease[1-4]
- For patients with NMIBC with high-risk tumors, SOC is TURBT followed by intravesical BCG or chemotherapy
  - While response rates to BCG are high, many patients recur within 1-5 years[5]
- While cystectomy is a SOC for BCG-unresponsive disease, many patients are unfit or refuse[1,2]
- EV is an ADC directed to Nectin-4, which is highly expressed in all stages of bladder cancer[6,7]
- EV alone and in combination with pembrolizumab is approved for the treatment of Ia/mUC[8]
- Preclinical models with intravesical administration showed EV was well-tolerated and demonstrated antitumor activity[9]
  - In repeat dose studies conducted at 24-fold the clinical dose, there were no detectable local or systemic toxicities with minimal and transient systemic exposure
  - Orthotopic models of NMIBC showed dose and concentration dependent anti-tumor activity
  - These models suggested a starting dose of 125 mg would be efficacious, well tolerated, and have minimal systemic exposure
- EV-104 (NCT05014139) is evaluating the intravesical administration of EV for patients with high-risk BCG-unresponsive NMIBC
- Here we present initial safety, tolerability, PK, and efficacy results for the first intravesically administered vedotin ADC

Enfortumab Vedotin Proposed Mechanism of Action



Methods

EV-104 Study Design



Primary endpoints	• Type, incidence, severity, seriousness, and relatedness of AEs • Type, incidence, and severity of laboratory abnormalities • Incidence of DLTs and cumulative safety per dose level
Key secondary endpoints	• Estimates of selected PK parameters • CR rate at any time on study and CR rates at 3, 6, 12, 18 and 24 months • Duration of CR, PFS, and cystectomy-free survival

EV-104 Dose Escalation Design

- Dose escalation phase aims to identify the MTD or recommended dose of intravesical EV at four dose levels
- Study design optimized to maximize intravesical drug concentration and limit urinary urgency with a 25 mL dose volume
- Approximately 18 patients will be treated across four dosing levels during dose escalation
- Escalation rules are guided by the modified toxicity probability interval design using a Bayesian model for "escalation", "stay", or "de-escalation"
- As of data cutoff (10 February 2023), 6 patients had been enrolled and received EV at the first two dose levels

Results

Key Demographic and Baseline Disease Characteristics

	EV 125 mg (N=4)	EV 250 mg (N=2)
Male sex, n (%)	3 (75.0)	2 (100.0)
Age (yrs), median (range)	71.0 (60.0-74.0)	78.0 (72.0-84.0)
White race, n (%)	4 (100.0)	1 (50.0)
ECOG PS, n (%)		
0	4 (100.0)	2 (100.0)
Disease stage at study entry, n (%)		
Carcinoma in situ (Tis)	2 (50.0)	2 (100.0)
Carcinoma in situ (Tis) w/ T1	1 (25.0)	0
Carcinoma in situ (Tis) w/ high grade Ta	1 (25.0)	0
Category of BCG failure, n (%)		
BCG-Relapsed	2 (50.0)	1 (50.0)
BCG-Refractory	2 (50.0)	1 (50.0)
Any histological variant(s), n (%)		
No	4 (100.0)	2 (100.0)
Reason for patient not undergoing cystectomy		
Patient refusal	4 (100.0)	2 (100.0)

Summary of Disposition

	EV 125 mg (N=4) n (%)	EV 250 mg (N=2) n (%)
Patients receiving any amount of EV	4 (100.0)	2 (100.0)
Patients on treatment	2 (50.0)	2 (100.0)
Patients off treatment	2 (50.0)	0
Reason for treatment discontinuation		
Completed treatment	1 (25.0)	0
Persistent disease	1 (25.0)	0
Patients on study	4 (100.0)	2 (100.0)

All 6 patients completed the DLT evaluable period.
No DLTs were observed for either 125 mg or 250 mg.

Treatment-Related Adverse Events

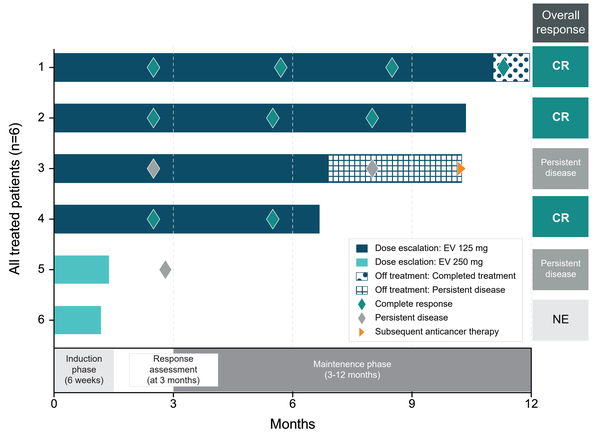
TRAEs by preferred term ≥2 of 6 total patients	EV 125 mg (N=4) n (%)		EV 250 mg (N=2) n (%)		Total (N=6) n (%)	
	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2
Patients with any event	2 (50.0)	1 (25.0)	1 (50.0)	1 (50.0)	3 (50.0)	2 (33.3)
Fatigue	2 (50.0)	0	0	1 (50.0)	2 (33.3)	1 (16.7)
Dry eye	2 (50.0)	0	0	0	2 (33.3)	0
Micturition urgency	1 (25.0)	0	1 (50.0)	0	2 (33.3)	0

- No grade ≥3 TRAEs
- No treatment-related SAEs
- No TRAEs leading to dose reduction or discontinuation

All blood PK analyses (ADC[a] and unconjugated MMAE) for patients treated at 125 mg were undetectable; complete PK data was not available for patients treated at 250 mg as of data cutoff.

[a]ADC refers to intact EV while unconjugated MMAE refers to the cytotoxic payload component of EV

Preliminary Efficacy of Intravesical EV



Per protocol, patient 3 (125 mg) with persistent disease at 3 months was allowed to stay on treatment until the 6-month disease assessment

At the time of data cutoff, patient 6 (250 mg) had not yet completed their 3-month evaluation and was considered non-evaluable

- 1 patient at 125mg completed all planned doses of EV
- Of the 5 efficacy-evaluable patients, 3 achieved a CR at the time of the data cutoff