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STUDY EV-103 COHORT H: ANTITUMOR ACTIVITY OF NEOADJUVANT TREATMENT WITH ENFORTUMAB VEDOTIN MONOTHERAPY IN PATIENTS WITH MUSCLE INVASIVE BLADDER CANCER WHO ARE CISPLATIN-INELIGIBLE

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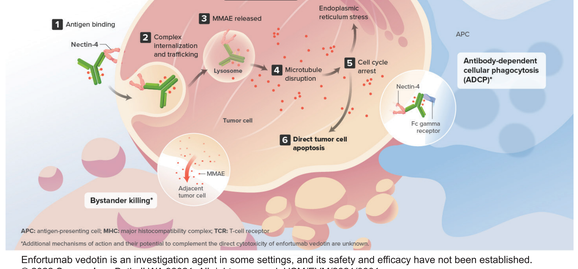
Background

- Cisplatin-ineligible patients do not have established neoadjuvant treatment options known to prolong survival prior to undergoing RC+PLND
  - pCR ranges from 36% to 42% for approximately 60% of patients with MIBC who are eligible for cisplatin-based chemotherapy[1–3]
- Efficacy and safety of EV was established in cisplatin-ineligible patients with previously treated locally advanced/metastatic UC and is approved by the FDA for this indication[4–7]
  - In a phase 3 trial, EV showed improved OS versus chemotherapy and a tolerable safety profile in patients with advanced UC previously treated with chemotherapy and PD-1/L1 inhibitor[8]
- This study shows preliminary data from Cohort H of the EV-103 phase 1b/2 trial in patients with MIBC who are cisplatin-ineligible and treated with neoadjuvant EV monotherapy

Enfortumab Vedotin Proposed Mechanism of Action[9–11]



Abbreviations

advanced UC: locally advanced or metastatic urothelial cancer; AE: Adverse events; DFS: Disease-free survival; DM: Diabetes mellitus; ECOG: Eastern Cooperative Oncology Group; EFS: Event-free survival; EV: Enfortumab vedotin; KN: Keynote; MDRD: Modification of Diet in Renal Disease; MIBC: muscle invasive bladder cancer; OS: Overall survival; PD-1/L1:Programmed cell death protein 1/programmed death-ligand 1; pCR: pathological Complete Response; pDS: pathological Downstaging; PROs: Patient-reported outcomes; RC+PLND: radical cystectomy + pelvic lymph node dissection; TCC: transitional cell carcinoma; TURBT: transurethral resection of bladder tumor; TEAEs: Treatment-emergent adverse events

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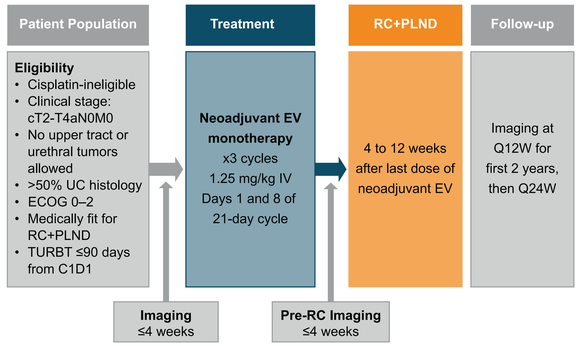
EV-103 Cohort H Study Design



- **Primary endpoint:** pCR rate by central pathology review
- **Secondary endpoints:** pDs rate (central review), EFS, DFS, OS, safety, PROs, biomarkers

Key Demographics and Disease Characteristics

Characteristic	Patients (N=22) n (%)
Median age (range), years	74.5 (56, 81)
Male sex, n (%)	20 (90.9)
White race, n (%)	22 (100.0)
Current or former smoker, n (%)	21 (95.5)
Median enrollment time from diagnosis (range), months	1.6 (1, 3)
ECOG performance status, n (%)	
0	13 (59.1)
1	8 (36.4)
2	1 (4.5)
Current stage, n (%)	
cT2N0	15 (68.2)
cT3N0	6 (27.3)
cT4aN0	1 (4.5)
Histology type, n (%)	
TCC only	15 (68.2)
TCC with squamous differentiation	3 (13.6)
TCC with other histologic variants	4 (18.2)
TCC+adenocarcinoma	1 (4.5)
TCC+micropapillary	2 (9.1)
TCC+sarcomatoid	1 (4.5)

Date of Data Cut: 9 Sept 2021

Reasons for Cisplatin-ineligibility

- Creatinine clearance ≥30 to <60 mL/min was the most common reason for cisplatin-ineligibility

	Patients (N=22) n (%)
Patients meeting at least one of the following Galsky criteria	22 (100.0)
Reason for cisplatin-ineligibility[a]	
Creatinine clearance <60 mL/min and ≥30 mL/min[b]	11 (50.0)
ECOG PS of 2	1 (4.5)
Grade ≥2 hearing loss	9 (40.9)
Creatinine clearance <60 mL/min and ≥30 mL/min and Grade ≥2 hearing loss	1 (4.5)

a The categories are mutually exclusive
b Estimated creatinine clearance per Cockcroft-Gault Criteria or 24-hr urine collection (local lab) or MDRD equation

Study Treatment

- 19/22 patients completed all 3 cycles of neoadjuvant EV
- All enrolled patients underwent surgery without delay

	EV Monotherapy (N=22)
Duration of neoadjuvant treatment[a] (months)	Median (Range) 2.1 (0.7–2.3)
Patients treated at[b]	n (%)
Neoadjuvant Cycle 1	22 (100.0)
Neoadjuvant Cycle 2	20 (90.9)
Neoadjuvant Cycle 3	19 (86.4)
Time from end of neoadjuvant EV to RC+PLND[c] (months)	Median (Range) 1.8 (1.0–2.7)
Bladder surgery not performed or delayed due to to TEAEs[d]	0
Patients on study	19 (86.4)
Patients off study	3 (13.6)
Reason off study: Death	3 (13.6)

a Study treatment includes neoadjuvant enfortumab vedotin and RC+PLND
b 21 patients underwent RC+PLND; 1 patient had partial cystectomy (included in pre-specified efficacy analysis)
c The time from the last dose of neoadjuvant EV to the date of surgery
d TEAEs are newly occurring or worsening AEs after the first dose through 30 days after the end of study treatment

Efficacy: Central Pathology Review

Pathological Response	Central Pathology Results (N=22) n (%) [95% Confidence Interval]
Pathological Complete Response Rate (defined as absence of any viable tumor tissue; ypT0 and N0)	8 (36.4) [17.2–59.3]
Pathological Downstaging Response Rate (defined as presence of ypT0, ypTis, ypTa, ypT1, and N0)	11 (50.0) [28.2–71.8]

Treatment Emergent Adverse Events

- Overall, 4 (18%) patients had Grade ≥3 EV-Related TEAEs
  - Grade 3 EV-related TEAEs included: asthenia, dehydration, erythema multiforme, hyperglycemia, post procedural urine leak, rash maculo-papular, small intestinal obstruction
- No EV-related Grade 4 TEAEs or deaths were observed
- 3 deaths occurred on the study:
  - Acute kidney injury
  - Cardiac arrest (related to RC+PLND)
  - Pulmonary embolism (related to RC+PLND)

Treatment-Related TEAEs* in ≥20% of patients (any Grade)	Patients (N=22) n (%)
Overall TRAEs	22 (100.0)
Fatigue	10 (45.5)
Alopecia	8 (36.4)
Dysgeusia	8 (36.4)
Diarrhea	6 (27.3)
Nausea	6 (27.3)
Peripheral sensory neuropathy	6 (27.3)
Dry eye	5 (22.7)
Rash maculo-papular	5 (22.7)

* TEAEs are newly occurring AEs or worsening AE after the first dose of study treatment through 30 days after the end of study treatment

Treatment-Emergent Adverse Events Leading to Dose Modification and Discontinuation

TEAEs	Patients (N=22) n (%)
TEAEs leading to EV dose interruption (elimination or delay)*	3 (13.6)
EV-related TEAEs leading to EV dose delay	2 (9.1)
Diarrhea (Grade 1)	1 (4.5)
Fatigue (Grade 2)	1 (4.5)
EV-related TEAEs leading to EV dose reduction	2 (9.1)
Dysgeusia (Grade 2)	1 (4.5)
Diarrhea (Grade 2)	1 (4.5)
EV-related TEAEs leading to EV discontinuation	3 (13.6)
Dehydration (Grade 3)	1 (4.5)
Erythema multiforme (Grade 3)	1 (4.5)
Rash maculo-papular (Grade 3)	1 (4.5)

* Dose elimination is when a scheduled dose is skipped; Dose delay is when a dose did not occur on the scheduled dosing cycle. One delay was due to inclement weather at site (unrelated).

Adverse Events of Special Interest[a]

- Most events were Grade 1 or 2 and resolved
- There was no preexisting DM for the 5 patients who had hyperglycemia

	Patients (N=22) n (%)	
	Any Grade	≥Grade 3
Peripheral neuropathy	8 (36.4)	0
Skin reaction[b]	14 (63.6)	2 (9.1)
Hyperglycemia (non-fasting)	5 (22.7)	3 (13.6)
Ocular disorder[c]	9 (40.9)	0
Infusion-related reactions (IRR)[d]	2 (9.1)	0

a Events are not mutually exclusive
b Skin reaction includes any rash and any severe cutaneous adverse reaction
c Ocular disorder include any blurred vision, any corneal disorders, and any dry eye
d IRR events include any systemic IRR, any local IRR, and any infusion site extravasation

Summary

- Neoadjuvant enfortumab vedotin showed promising antitumor activity in patients with MIBC ineligible for cisplatin as shown by pCR of 36% and pDS of 50%
- All patients were able to undergo surgery and there was no delay in surgery due to neoadjuvant enfortumab vedotin
- The observed safety profile of neoadjuvant enfortumab vedotin monotherapy in patients with cisplatin-ineligible MIBC is consistent with the known AE profile of enfortumab vedotin in other settings
  - Overall incidence of Grade 3 or higher treatment-related AEs was low
  - No new safety concerns were identified
- This first disclosure of data supports the ongoing phase 2 and 3 programs evaluating enfortumab vedotin alone or in combination with pembrolizumab in MIBC (EV-103 Cohort L, KN-905, KN-B15)