Study EV-103: Neoadjuvant Treatment With Enfortumab Vedotin Monotherapy in Cisplatin-Ineligible Patients (Pts) With Muscle Invasive Bladder Cancer (MIBC): Updated Results for Cohort H

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Objectives

To provide updated results, including 1-year EFS, subsequent cancer-related therapy, and safety and tolerability, from Cohort H of study EV-103, which evaluated neoadjuvant EV treatment in patients with MIBC who were ineligible to receive cisplatin therapy.

Conclusions

Neoadjuvant EV monotherapy treatment showed promising results for antitumor activity and EFS with a manageable safety profile in cisplatin-ineligible patients with MIBC

All patients were able to undergo surgery with no delays due to neoadjuvant EV-related TEAEs in this understudied population

The observed safety profile of neoadjuvant EV monotherapy in this cohort is consistent with the known AE profile of EV in other settings

These results support ongoing phase 2 and 3 programs evaluating EV alone or in combination with pembrolizumab in MIBC
- EV-103 Cohort L
- KEYNOTE-905
- KEYNOTE-B15

Abbreviations

AE: Adverse event; CrCl: creatinine clearance; DFS: Disease-free survival; ECOG PS: Eastern Cooperative Oncology Group performance status; EFS: Event-free survival; EV: enfortumab vedotin; la/mUC: locally advanced or metastatic urothelial cancer; 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; RC+PLND: radical cystectomy + pelvic lymph node dissection; TCC: transitional cell carcinoma; TEAE: treatment-emergent adverse event; TURBT: transurethral resection of bladder tumor

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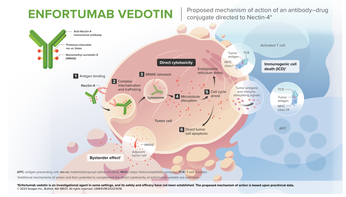
Background

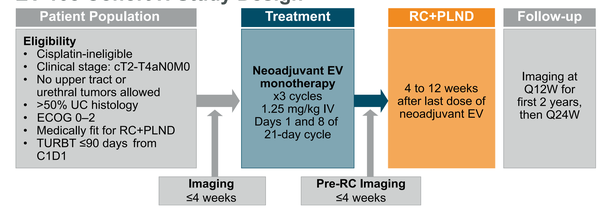
- Patients with MIBC who are ineligible for cisplatin therapy have no established neoadjuvant treatment options known to prolong survival prior to undergoing RC+PLND
  - pCR rate ranges from 36% to 42% of patients with MIBC who are eligible for cisplatin-based chemotherapy[1-3]
- The efficacy and safety of EV has been established in patients with previously treated urothelial cancer[4-7]
  - In a phase 3 study, EV showed improved overall survival vs investigator-chosen chemotherapy (standard docetaxel, paclitaxel, or vinflunine) and a tolerable safety profile in patients with advanced urothelial cancer previously treated with a platinum agent and a PD-1/L1 inhibitor[8]
- EV and pembrolizumab in combination was given US accelerated approval in the first-line treatment of cisplatin-ineligible patients with previously untreated la/mUC based on the EV-103 Cohort K and Dose Escalation/Cohort A results
- In Cohort H of the EV-103 phase 1b/2 study, preliminary results, including pCR and pDS rates, showed antitumor activity in cisplatin-ineligible patients with MIBC who received neoadjuvant EV treatment[9]
- Here we report updated results, including EFS, subsequent cancer-related therapy, and safety and tolerability, from this study cohort

Proposed Mechanism of Action



Methods

EV-103 Cohort H Study Design



Results

Reasons for Cisplatin Ineligibility

- CrCl ≥30 to <60 mL/min was the most common reason for cisplatin-ineligibility (n=11; 50.0%), followed by grade ≥2 hearing loss (n=9, 40.9%), CrCl ≥30 to <60 mL/min and grade ≥2 hearing loss (n=1; 4.5%), and ECOG PS of 2 (n=1; 4.5%)

Key Demographic and Baseline Disease Characteristics

Characteristic	Patients (N=22)
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 PS, n (%)	
0	13 (59.1)
1	8 (36.4)
2	1 (4.5)
Current stage, n (%)[a]	
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)

[a]Defined as the most recent stage prior to study enrollment

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 EV treatment (months)	Median (range) 2.1 (0.7-2.3)
Patients treated at[a]	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 (months)[b]	Median (range) 1.8 (1.0-2.7)
Bladder surgery not performed or delayed due to EV-related TEAEs	0
Patients on study	17 (77.3)
Patients off study	5 (22.7)
Reason off study: Death	5 (22.7)

[a]21 patients underwent RC+PLND; 1 patient had partial cystectomy (included in prespecified efficacy analysis)
[b]The time from the last dose of neoadjuvant EV to date of RC+PLND

Antitumor Activity: Central Pathology Review

- As of data cutoff (17JAN2023), of 8 patients with a pCR, 7 patients continue to be disease-free, and 1 patient had died due to an acute kidney injury that was considered unrelated to study treatment

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

Event-Free Survival by Investigator

- Median EFS has not been reached
- The EFS rate at 12 months was 76.4% (95% CI, 52.2, 89.4)

Subsequent Cancer-Related Therapy

	Patients (N=22) n (%)
Patients receiving first subsequent cancer-related therapy	8 (36.4)
Systemic therapy for residual MIBC/high risk MIBC at cystectomy	4 (18.2)
Pembrolizumab	2 (9.1)
Carboplatin-based therapy	1 (4.5)
Erdafitinib	1 (4.5)
Systemic therapy for progressive disease	1 (4.5)
Carboplatin-based therapy with avelumab	1 (4.5)
Other	3 (13.6)
Radiation therapy for second malignancy	1 (4.5)
Surgery: laparoscopic distal pancreatectomy	1 (4.5)
Surgery: partial cystectomy with prostatectomy	1 (4.5)

Treatment-Emergent Adverse Events

- 4 patients (18.2%) had EV-related grade 3 TEAEs; no EV-related grade 4 or 5 TEAEs occurred
  - Dehydration, erythema multiforme, hyperglycemia, postprocedural urine leak, rash maculopapular, and small intestinal obstruction
- 3 patients died due to AEs:
  - Acute kidney injury: unrelated to study treatment (occurred >30 days after RC+PLND and last EV dose)
  - Cardiac arrest: related to RC+PLND (occurred <30 days after RC+PLND and >30 days after last EV dose)
  - Pulmonary embolism: related to RC+PLND (occurred >30 days after RC+PLND and last EV dose)

EV-Related Treatment-Emergent Adverse Events

EV-Related TEAEs in ≥20% of patients (any grade)	Patients (N=22), n (%)
Fatigue	10 (45.5)
Dysgeusia	8 (36.4)
Alopecia	7 (31.8)
Diarrhea	6 (27.3)
Nausea	6 (27.3)
Peripheral sensory neuropathy	6 (27.3)
Dry eye	5 (22.7)
Rash maculopapular	5 (22.7)

EV-Related Treatment-Emergent Adverse Events Leading to EV Dose Modification and Discontinuation

	Patients (N=22), n (%)
EV-related TEAEs leading to EV dose interruption[a]	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 maculopapular (grade 3)	1 (4.5)

[a]Dose interruption includes dose elimination and dose delay. Dose elimination occurred when a scheduled dose was skipped; dose delay was when a dose was not administered on the scheduled dosing cycle.

Adverse Events of Special Interest for EV

- Most events were grade 1 or 2

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

Note: Events are not mutually exclusive
[a]Skin reaction includes any rash and any severe cutaneous adverse reaction
[b]Ocular disorder includes any blurred vision, any corneal disorders, and any dry eye
[c]These events include any systemic or local infusion-related reaction and any infusion site extravasation

Time to Onset and Resolution for Adverse Events of Special Interest for EV

	Patients (N=22)		
	Total number of events[a]	Median time to first onset of any event,[a] months (range)	Median time to resolution[b] of any event, months (range)
Skin reaction	18	0.5 (0.2, 1.2)	0.8 (0.1, 4.6)
Peripheral neuropathy	9	1.3 (0.3, 1.8)	2.6 (0.5, 5.5)
Hyperglycemia	5	0.7 (0.3, 0.7)	0.8 (0.03, 3.7)

[a]Patients could have had more than 1 event
[b]Resolution defined as recovered/resolved or recovered/resolved with sequelae or a return to baseline grade or better at the last assessment

Event Resolution:
- Skin reaction events: 100% resolved
- PN events: 44% resolved
- Hyperglycemia events: 100% resolved