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

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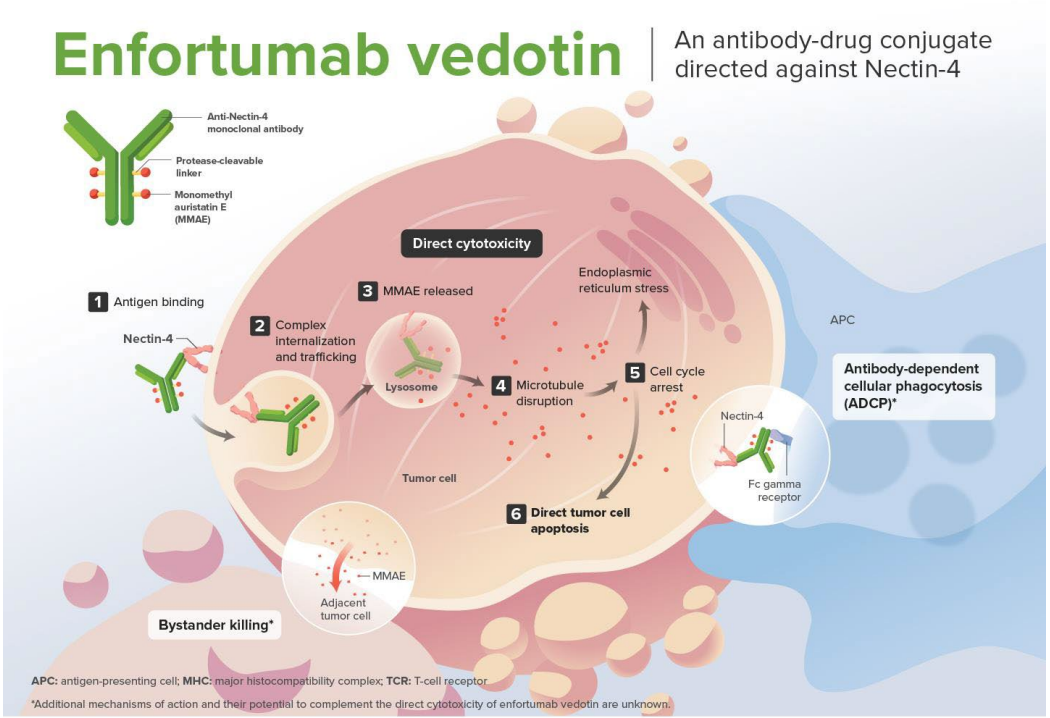
Background

- Cisplatin-ineligible patients do not have established neoadjuvant treatment options known to prolong survival prior to undergoing radical cystectomy and pelvic lymph node dissection (RC+PLND)
  - For patients who are eligible for cisplatin-based chemotherapy, pCR ranges from 36% to 42%1,2
- Efficacy and safety of EV was established in cisplatin-ineligible patients with previously treated advanced UC and is approved by the FDA3–6
  - In a phase 3 trial, EV showed improved OS versus chemotherapy and a tolerable safety profile in patients withadvanced UC previously treated with chemotherapy and PD-1/L1 inhibitor7
- This study shows preliminary data from Cohort H of the EV-103 phase 1b/2 trial in patients with muscle invasive bladder cancer (MIBC) who are cisplatin-ineligible and treated with neoadjuvant EV monotherapy

References: 1. Grossman et al. NEJM. 2003;349:859; 2. Pfister, et al. Eurol Urol. 2021;79:214;;3. Friedlander et al. ASCO 2021; Abstract No. 4528; 4. Yu et al. Lancet Oncol. 2021;22:872-82; 5. Rosenberg et al. J Clin Oncol. 2019;37;2592-2600; 6. Seagen Inc., Press release. Feb 19, 2020; 7. Powles et al. NEJM. 2021;384:1125-1135

EV: Enfortumab vedotin; advanced UC: 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; RC+PLND: Radical cystectomy and pelvic lymph node dissection

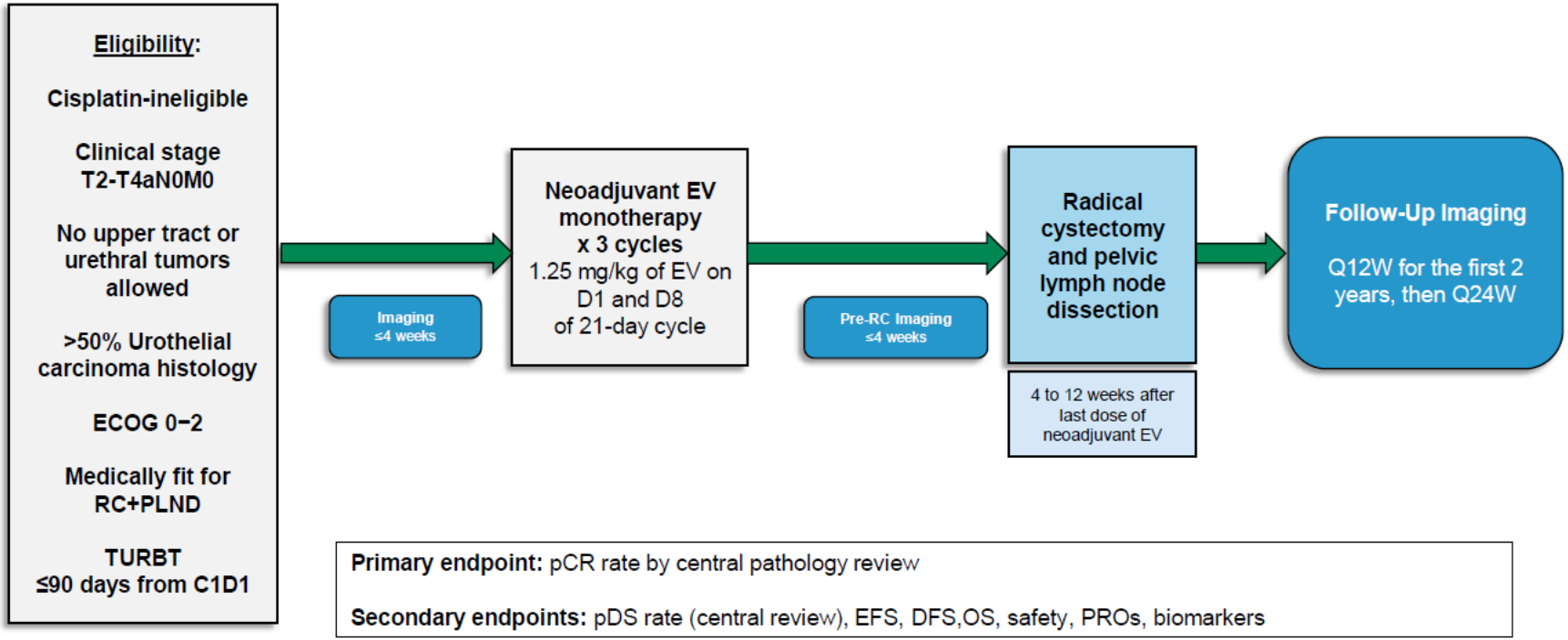
Enfortumab Vedotin Proposed Mechanism of Action



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

Challita-Eid et al. Cancer Res. 2016;76:3003-3013; Doronina et al. Nat Biotech. 2003;21:778-784; Liu et al. AACR. 2020; Abstract No. 6772, Poster No. 5581

EV-103 Cohort H Study Design



DFS: Disease-free survival; ECOG: Eastern Cooperative Oncology Group; EFS: Event-free survival; EV: Enfortumab vedotin; OS: Overall survival; pCR: pathological Complete Response rate; pDS: pathological Downstaging; RC+PLND: radical cystectomy + pelvic lymph node dissection; PROs: Patient-reported outcomes; TURBT: transurethral resection of bladder tumor

Key Demographic and Disease Characteristics

	Cohort H (N=22)
Male sex, n (%)	20 (90.9)
Median age (range), years	74.5 (56–81)
White race, n (%)	22 (100)
Current or former smoker, n (%)	21 (95.5)
Median enrollment time from diagnosis (range), months	1.6 (1–3)
ECOG performance status	
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 (%)	
Transitional cell carcinoma (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)

Data cut date: 9 Sep 2021

Reasons for Cisplatin-ineligibility in Cohort H

- Creatine clearance 30–60 mL/min was the most common reason for cisplatin-ineligibility

	Cohort H (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
ECOG PS: Eastern Cooperative Oncology Group performance status

Data cut date: 9 Sep 2021

Study Treatment

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

	EV Mono (N=22)
	Median (Range)
Duration of neoadjuvant treatment[a] (months)	2.1 (0.7–2.3)
Patients treated at[b]	n (%)
Neoadjuvant Cycle 1	22 (100)
Neoadjuvant Cycle 2	20 (91)
Neoadjuvant Cycle 3	19 (86)
	Median (Range)
Time from end of neoadjuvant EV to RC+PLND[c] (months)	1.8 (1.0–2.7)
Bladder surgery not performed or delayed due to TEAEs[d]	0
	n (%)
Patients on study	19 (86)
Patients off study	3 (14)
Reason off study: Death	3 (14)

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

EV: Enfortumab Vedotin; RC+PLND: Radical cystectomy plus pelvic lymph node dissection; TEAEs: Treatment-emergent adverse events

Data cut date: 9 Sep 2021

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 Rate (defined as presence of ypT0, ypTis, ypTa, ypT1, and N0)	**11 (50.0%)** [28.2–71.8]

Data cut date: 9 Sep 2021

Safety: Treatment Emergent Adverse Events

EV-related TEAEs seen in ≥20% patients by preferred term	EV Mono (N=22)
Overall (all Grades)	22 (100)
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
EV: Enfortumab vedotin; RC+PLND: Radical cystectomy plus pelvic lymph node dissection; TEAEs: Treatment-emergent adverse events

Data cut date: 9 Sep 2021

- 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)

Safety: TEAEs Leading to Dose Modification and Discontinuation

- There were no dose reductions due to peripheral neuropathy

TEAEs	EV Mono (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).
EV: Enfortumab vedotin; TEAEs: Treatment-emergent adverse events

Data cut date: 9 Sep 2021

Safety: Adverse Events of Special Interest

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

	EV Mono N=22	
	Any Grade n (%)	Grade ≥3 n (%)
Peripheral neuropathy	8 (36.4)	0
Skin reaction*	14 (63.6)	2 (9.1)
Hyperglycemia (non-fasting)	5 (22.7)	3 (13.6)
Ocular disorder**	9 (40.9)	0
Infusion-related reactions (IRR)‡	2 (9.1)	0

Events are not mutually exclusive.
*Skin reaction includes any rash and any severe cutaneous adverse reaction
**Ocular disorder include any blurred vision, any corneal disorders, and any dry eye
‡IRR events include any systemic IRR, any local IRR, and any infusion site extravasation
DM: Diabetes mellitus EV: Enfortumab vedotin; IRR: Infusion-related reactions

Data cut date: 9 Sep 2021

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 signals 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)

AE: Adverse events; EV: Enfortumab vedotin; KN: Keynote; MIBC: Muscle invasive bladder cancer; pCR: pathological complete response; pDS: pathological downstaging

Acknowledgements

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