Study EV-103 Cohort L: Perioperative treatment w/ enfortumab vedotin (EV) monotherapy in cisplatin (cis)-ineligible patients (pts) w/ muscle invasive bladder cancer (MIBC)

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Background

- Up to 25% of all patients diagnosed with urothelial cancers present with MIBC[1]
- Current SOC for patients with MIBC is neoadjuvant cisplatin-based chemotherapy followed by surgery; in high-risk patients adjuvant therapy may be recommended[2,3]
  - Up to 50% of patients may be cisplatin-ineligible where SOC is surgery alone[4]
- Due to high rates of recurrence in cisplatin-ineligible patients treated with surgery alone, there remains a significant unmet need for novel therapies in this setting[4]
- Previously neoadjuvant EV in cisplatin-ineligible MIBC showed encouraging antitumor activity[5]
  - Pathological complete response rate of 36%, pathological downstaging rate of 50%
  - No new safety signals, no delays to surgery, and low incidence of grade ≥3 EV-related TEAEs
- EV-103 Cohort L (NCT03288545) examines a perioperative approach consisting of both neoadjuvant and adjuvant EV in cisplatin-ineligible patients with MIBC

EV: enfortumab vedotin; **MIBC:** Muscle Invasive Bladder Cancer; **SOC:** Standard of Care; **Surgery:** Radical Cystectomy and Pelvic Lymph Node Dissection; **TEAE:** treatment-emergent adverse events.

1. Aragon-Ching JB. ASCO Educ Book. 2018. **2.** Milowsky ML. JCO. 2016: 1945-52. **3.** Chang SS. J Urol. 2017: 552-559. **4.** Galsky MD. Future Oncol. 2021: 3137-50. **5.** Petrylak D. ASCO 2022: Abstract 4582.

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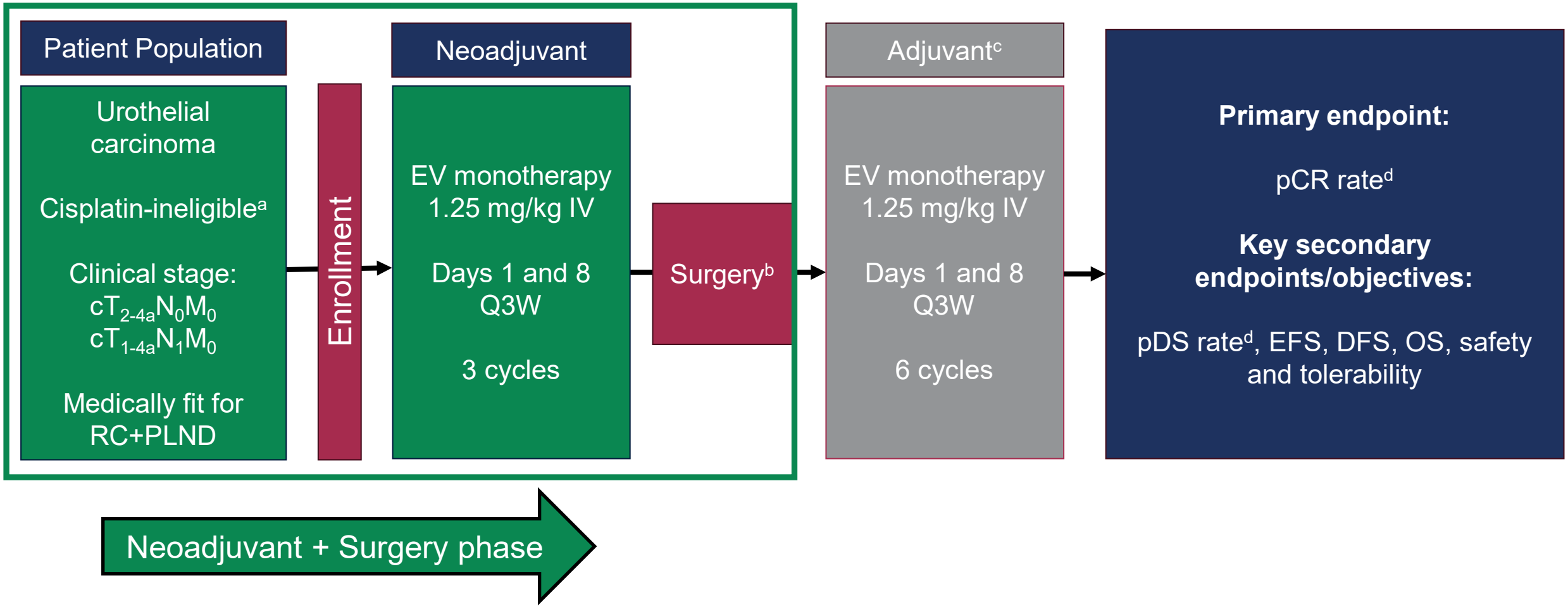
EV-103 Cohort L: Perioperative EV in Cisplatin-Ineligible MIBC



CTCAE: Common Terminology Criteria for Adverse Events; **DFS:** disease-free survival; **ECOG PS:** Eastearn Cooperative Oncology Group Performance Status; **EFS:** event free survival; **EV:** enfortumab vedotin; **IV:** intravenous; **GFR:** glomerular filtration rate; **NYHA:** New York Heart Association; **OS:** Overall Survival; **pCR:** pathological complete response; **pDS:** pathological downstaging; **Q3W:** every 3 wks; **RC+PLND:** radical cystectomy, pelvic node dissection.

[a]Cisplatin ineligibility: Galsky criteria ≥1 of: GFR <60 and ≥30mL/min, ECOG PS of 2, NCI CTCAE Version 4.03 grade ≥2 hearing loss, or NYHA Class III heart failure.

[b]Surgery phase: RC+PLND and 30 day post-operative period.

[c]Adjuvant phase begins 8 weeks after surgery.

[d]per central pathology review.

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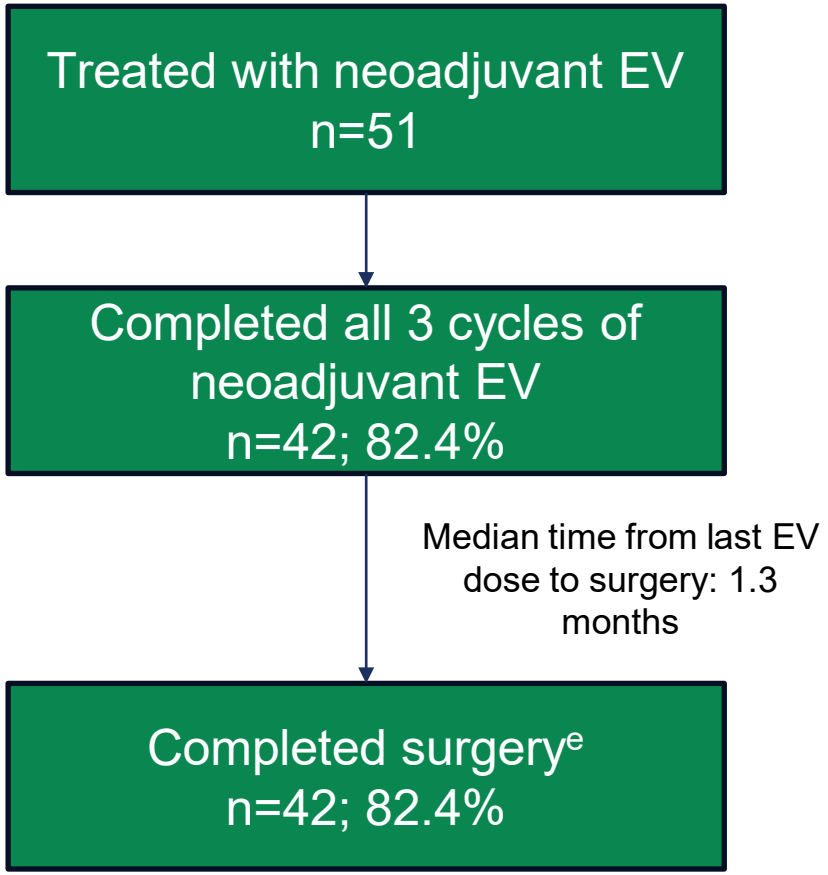
Baseline Patient Characteristics and Disposition

Over 80% of patients completed 3 cycles of neoadjuvant EV and surgery

Characteristics	Cohort L (n=51[a])
Male, n (%)	39 (76.5)
Median age (range), years	74.0 (54, 85)
ECOG PS 0-1, n (%)	49 (96.1)
Baseline stage[b], n (%)	
cT2N0	29 (56.9)
cT3N0	13 (25.5)
cT4N0	4 (7.8)
cT2-3N1[c]	5 (9.8)
Creatinine clearance (CrCl) <60 and ≥30 mL/min[d]	23 (45.1)



ECOG PS: Eastern Cooperative Oncology Group Performance Status; **EV:** enfortumab vedotin; **MDRD:** modification of diet in renal disease; **RC+PLND:** radical cystectomy, pelvic node dissection.

[a]52 pts enrolled; 51 treated with neoadjuvant EV + RC+PLND; 1 did not receive EV.

[b]Most recent stage prior to study entry.

[c]cT_2N_1 (n=4), $cT_{2\text{-}3}N_1$ (n=1)

[d]CrCl determined by Cockcroft-Gault formula, MDRD equation or 24-hour urine collection.

[e]Nine patients did not complete RC+PLND: adverse event (2), physician decision (1), disease progression (2), patient refusal (3), patient consent withdrawal (1).

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Pathological Complete Response Rate (pCR)

pCR of 34%; pDS of 42%

Pathological Response	Central Pathology Review (n=50[a]) n (%) [95% CI[b]]
pCR (defined as absence of viable tumor tissue: ypT0N0)	**17 (34.0)** [21.2, 48.8]
pDS[c] (defined as patients with <ypT2, including pT0, pTis, pTa, pT1, and N0)	**21 (42.0)** [28.2, 56.8]

CI: confidence interval; **CR:** complete response; **pCR:** pathological complete response; **pDS:** pathological downstaging.
[a]One patient achieved clinical CR and did not undergo surgery and was excluded from pCR and pDS analyses.
[b]Computed with the Clopper-Pearson method.[1]
[c]pDS included as key secondary endpoint.

1. Clopper, C.; Pearson, E. S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". *Biometrika*. 26 (4): 404–413.

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Safety: EV-related TEAEs in the Neoadjuvant + Surgery Phase

EV-related TEAEs were generally manageable and there were no surgical delays

EV-related TEAEs[a] (n=51) n (%)		
	Any grade	Grade ≥3
Overall	46 (90.2)	20 (39.2)
Fatigue	27 (52.9)	1 (2.0)
Rash maculo-papular	16 (31.4)	6 (11.8)
Nausea	15 (29.4)	-
Alopecia	14 (27.5)	-
Peripheral sensory neuropathy	14 (27.5)	1 (2.0)
Pruritis	12 (23.5)	-
Hyperglycemia	7 (13.7)	6 (11.8)

- The majority of EV-related AESIs[b] were ≤grade 2
  - 56.9% of patients (29/51) had skin reactions; 1 patient died due to Stevens-Johnson syndrome
  - 33.3% of patients (17/51) had peripheral neuropathy
- No delays to surgery due to EV-related TEAEs
- Most common ≥grade 3 surgery-related AEs were anemia, ileus, and urinary tract infection

AE: adverse event; **AESI:** Adverse event of special interest; **EV:** enfortumab vedotin; **GR:** grade; **RC+PLND:** radical cystectomy, pelvic node dissection; **Surgery:** RC+PLND; **TEAE:** treatment-emergent adverse event

[a]In ≥20% (any grade) or ≥5% (Gr≥3); EV and RC-relatedness determined by investigator; TEAEs in neoadjuvant and RC period were any event occurring after first dose of EV. through 30 days after last dose of neoadjuvant EV and/or surgery.

[b]Predefined AESIs: ocular disorders, hyperglycemia, peripheral neuropathy, skin reactions (rashes or subcutaneous adverse reactions), infusion-related reactions. 4 patients (7.8%) had a Gr3 and 2 patients (3.9%) had a Gr4 hyperglycemia EV-related TEAE. 1 pt (2.0%) had a Gr3 peripheral neuropathy EV-related TEAE. 9 patients (17.6%) had a Gr3 and 1 patient (2.0%) had a Gr5 skin reaction EV-related TEAE.

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Authors' Conclusions

- EV continues to show promising antitumor activity in cisplatin-ineligible patients with MIBC
  - pCR of 34%; pDS of 42%
  - Results consistent with EV-103 Cohort H
- Safety profile of EV was similar to previously reported data from EV in MIBC and la/mUC[1-4]
  - No new safety signals; but close monitoring for toxicities remains important
  - No surgeries were delayed due to EV-related TEAEs
- This first data disclosure from EV-103 Cohort L supports the ongoing phase 3 programs evaluating EV in combination with pembrolizumab in MIBC (KN-905, KN-B15)
  - Additional follow-up will allow characterization of EFS, DFS, and OS data from Cohort L

DFS: disease free survival; **EFS:** event-free survival; **EV: e**nfortumab vedotin; **la/mUC:** locally advanced/metastatic urothelial cancer; **MIBC:** Muscle Invasive Bladder Cancer; **OS:** Overall Survival; **pCR:** pathological complete response; **pDS:** pathological downstaging; **TEAEs:** Treatment emergent adverse events.

1. O'Donnell PH. J Clin Oncol. 2023: 4107-17. **2.** Powles T. N Engl J Med. 2021: 1125-35. **3.** Yu EY. Lancet Oncol. 2021: 872-882. **4.** Petrylak D ASCO-GU 2022: Abstract 435.

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