Practical Management of Novel Bladder Cancer Therapy with Antibody-Drug Conjugates and Immunotherapies

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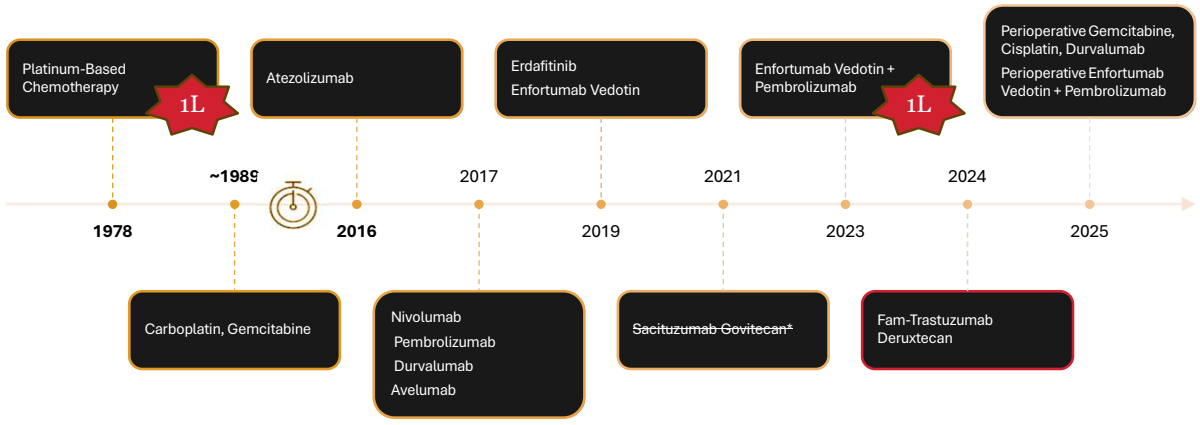
Disclosures

- No relevant disclosures

Outline

- Introduction and history of bladder cancer treatment
- Review mechanism of action of Enfortumab Vedotin + Pembrolizumab (EV/Pembro)
- Key toxicities associated with EV/Pembro
  - Skin toxicity
  - Peripheral Neuropathy
  - Hyperglycemia
- Principles of toxicity management and supportive care

Introduction



Enfortumab Vedotin + Pembrolizumab

EV-302, 2024

1L mUC
Established EV/Pembro as the preferred standard of care over platinum-containing chemotherapy
Median OS 31.5 vs 16.1 months, HR 0.47

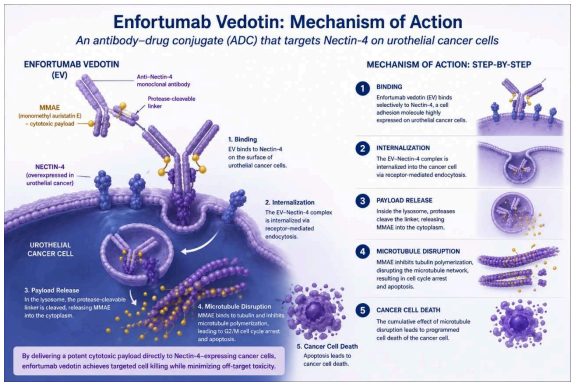
EV-303, 2025

Cisplatin-ineligible MIBC
2-year EFS 74.7 vs 39.4%, HR 0.40
OS HR 0.50 pCR 57.1% vs 8.6%

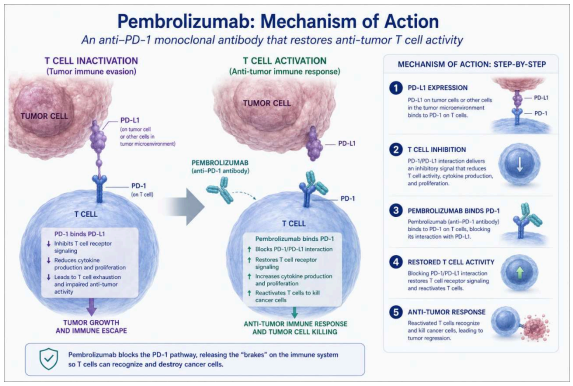
EV-304, 2026

Cisplatin-eligible MIBC
2-year EFS 79.4 vs 66.2%, HR 0.53
OS HR 0.65, pCR 55.8% vs 32.5%

Enfortumab Vedotin (ADC)



Pembrolizumab (Immunotherapy)



Other ADCs in Bladder Cancer

HER2-Targeted

- Trastuzumab deruxtecan (T-Dxd) — approved for HER2+ solid tumors
- Disitamab vedotin — in clinical trials

TROP2-Targeted

- Sacituzumab govitecan (SG) — Withdrawn
- Sacituzumab tirumotecan — in clinical trials

Emerging

- Izalontamab brengitecan — EGFR-HER3 bispecific dual ADC

Other Immune-Based Therapies

FDA Approved

Anktiva
Nogapendekin alfa inbakicept-pmln (IL-15 superagonist)

Adstiladrin
Nadofaragene firadenovec-vncg (gene therapy)

In Trials / Not Yet Approved

- Sasanlimab + BCG
- Durvalumab + BCG
- Cretostimogene grenadenorepvec (viral gene therapy)

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Novel Therapy = Novel Toxicities

EV Toxicity Category	Any Grade	Grade ≥3
Skin Toxicity	70%	17%
Peripheral Neuropathy	50–67%	5–7%
Hyperglycemia	5–11%	~6%
Ocular Disorders	Up to 46%	Rare
Dysgeusia	~42%	—

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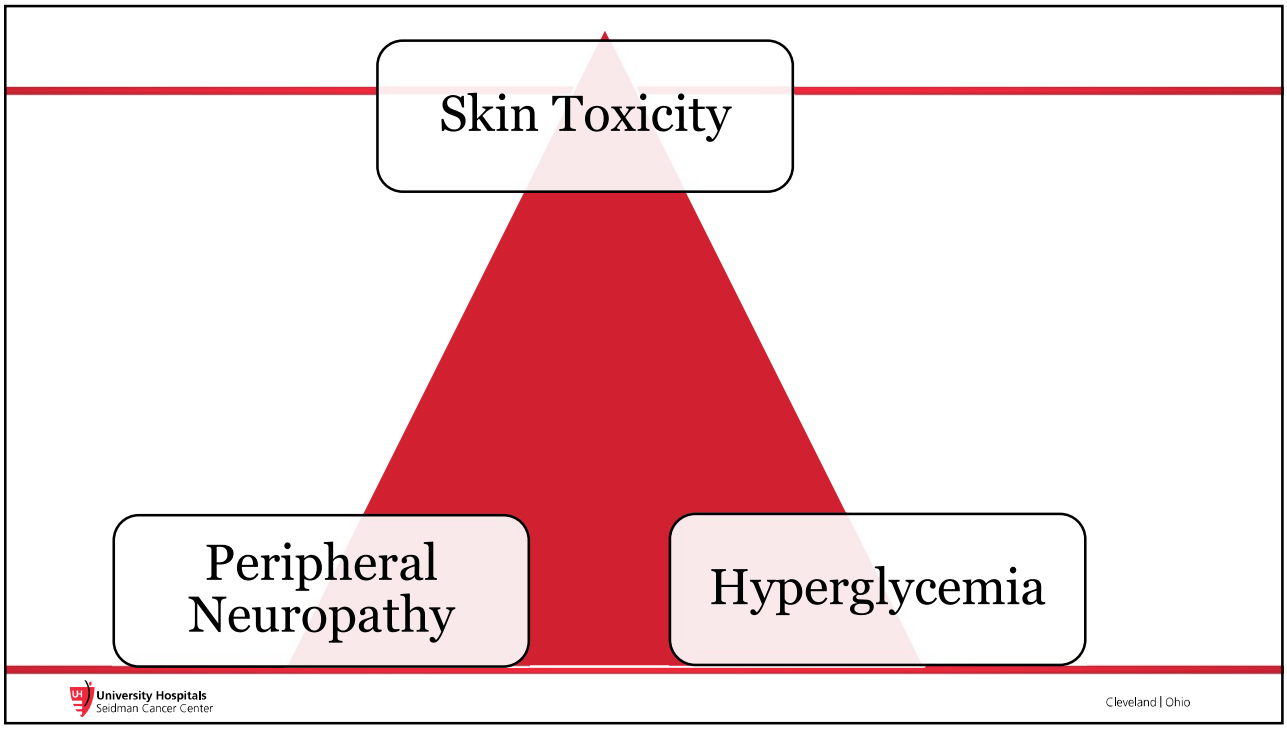
Other common AEs: Fatigue (56%), decreased appetite (52%), alopecia (50%), nausea (45%), diarrhea (42%)

Immune-Mediated Adverse Events

- Dermatitis
- Pneumonitis
- Colitis
- Endocrinopathies
- Hepatitis
- Nephritis



Skin Toxicity

- Rash, pruritus, sores, blistering, peeling of the skin
- Incidence: 70% any grade, 17% grade ≥3
- Higher with EV/Pembro combination vs EV monotherapy (56%, 12% grade ≥3)
- Early skin toxicity may predict better outcomes with EV
- Most reactions are manageable with dose modifications
- Median onset of severe reactions: 1.7 months (range 0.1–17.2)

SJS/TEN WARNING:
Can be fatal. Occurs predominantly during first cycle. Immediately hold EV; permanently discontinue for confirmed SJS/TEN.

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Skin Toxicity: Differentiation

EV-related rash vs immune-mediated skin reactions — accurate attribution guides whether to hold EV, pembro, or both.

Feature	Favors EV	Favors Pembrolizumab
Timing	<2 weeks from dosing	>6 weeks from dosing
Distribution	Intertriginous / flexural (SDRIFE pattern)	Generalized distribution
Histology / IHC	Ring mitosis Intercellular IgG	Lichenoid pattern

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Skin Toxicity: Management

Grade	Description	EV/Pembro Intervention	Management
Grade 1	<10% BSA +/- Mild symptoms	Continue and closely monitor	Topical steroids Oral antihistamines Skincare, emollients
Grade 2	10-30% BSA Limiting iADL Or >30% +/- Mild symptoms	Consider holds of EV and/or pembro Consider dose reduction of EV*	Consider dermatology referral Consider oral steroids
Grade 3	>30% BSA Moderate/severe symptoms Limiting ADL	HOLD EV and/or Pembro Resume EV when Grade 1 or better Strongly consider dose reduction	Dermatology referral Oral steroids
Grade 4 SJS TEN	Severe Requiring hospitalization and urgent intervention	HOLD EV/P Discontinue EV and/or pembro	Hospital admission Urgent dermatology consult

Sources: CTCAE v5; EV Manufacturer Guidelines; 2021 ASCO irAE Guidelines..

Peripheral Neuropathy

- Incidence: 50–67% any grade, 5–7% grade ≥3 in phase III rials
- **#1 reason for EV discontinuation (15% of patients in EV-302)**
- Sensory: numbness, tingling, burning or stabbing pain
- Motor: weakness, loss of coordination, gait changes
- Median onset: ~2.5 months
- Baseline assessment is critical — always ask about fine motor tasks AND walking

Peripheral neuropathy led to dose interruption, reduction, or discontinuation in a significant proportion of patients. Early recognition and proactive dose modification are essential.

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Peripheral Neuropathy: Management

Grade	Description	EV Dose Modification	Management
Grade 1	Asymptomatic	Continue and closely monitor	Patient Education
	Intermittent sensory symptoms not affecting iADL	Consider early EV dose reduction	Consider PT/OT evaluation Consider early medication intervention
Grade 2	Moderate symptoms Limiting iADL	HOLD EV Resume when at grade 1 or better Strongly consider dose reduction Consider irAE workup	Consider medications (duloxetine, gabapentinoid) PT/OT referral
Grade 3	Severe symptoms Limiting ADL	Discontinue EV Consider hold/discontinuation of pembrolizumab	Additional symptomatic medications ADL/HH assistive devices
Grade 4	Life-threatening	Discontinue EV and/or pembro	Hospital admission
Grade 5	Death		

Sources: CTCAE v5; EV PDI; Brower et al, 2024

Hyperglycemia

- Elevated blood glucose levels
- Incidence: 5-13% any grade, ~6% grade 3 or higher
- No significant difference in incidence between EV and EV/Pembro combination
- Screen baseline glucose, and check with each dose of EV

DKA Warning: Rare but potentially fatal!

- Driven by severe insulin resistance
- **Can occur in patients WITHOUT preexisting diabetes**
- Extreme insulin requirements reported: 800–7,200 units/day
- Typical onset: within 2 weeks of dosing
- Monitor for multiorgan dysfunction syndrome

Hyperglycemia: Management

Blood Glucose level	EV Dose Interventions	Management
<250 mg/dL	Continue	Patient education Collaboration with PCP/Endocrine
250 mg/dL or higher	Hold until <250 Resume at same dose	Insulin in clinic Consider referral to endocrinology

Key Takeaways

01 EV/Pembro is the new established front-line standard of care for bladder cancer

02 Novel therapies introduce novel toxicity profiles

03 Accurate toxicity attribution guides optimal management in combination therapy

04 Dose modifications and interruptions improve tolerability while maintaining continuity

05 Multidisciplinary collaboration is critical to optimizing patient outcomes

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Thank you!

Questions?
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Resources

Astellas. (2026). Informational Resource for Peripheral Neuropathy during treatment with Padcev. Retrieved from https://www.padcevhcp.com/resources

Astellas. (2026). Informational Resource for Skin Reactions during treatment with Padcev. Retrieved fromhttps://www.padcevhcp.com/resources

Brower, McCoy, Ahmad, Eitman, Bowman, Rembisz, Milowsky. (2024). Managing potential adverse events during treatment with enfortumab vedotin + pembrolizumab in patients with advanced urothelial cancer, Frontiers in Oncology, 14. doi 10.3389/fonc.2024.1326715

Enfortumab Vedotin. (2019). Prescribing information. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761137s029lbl.pdf

Galsky, M. (2026). Phase III KEYNOTE-B15/EV-204 study data. Abstract LBA630. 2026 ASCO GU Symposium

Hoimes, Flaig, Milowsky, Friedlander et al. (2022). Enfortumab vedotin plus pembrolizumab in previously untreated advanced urothelial cancer. *Journal of Clinical Oncology, 41*(3) doi 10.1200.JCO.22.01643

Pembrolizumab. (2014). Prescribing information. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s066lbl.pdf

Sayyid, R. (2024). ESMO 2024: Pre-treatment risk factors for enfortumab vedotin-induced peripheral neuropathy in patients with advanced urothelial carcinoma: Analysis of UNITE. https://www.urotoday.com/conference-highlights/esmo-2024/esmo-2024-bladder-cancer/154857-esmo-2024-pre-treatment-risk-factors-for-enfortumab-vedotin-induced-peripheral-neuropathy-in-patients-with-advanced-urothelial-carcinoma-analysis-of-unite.html#:~:text=Peripheral%20neuropathy%20is%20a%20frequent%2C%20dose%2Dlimiting%20toxicity,dose%20alteration%20event%20due%20to%20this%20neuropathy

Schneider, Naidoo, Santornasso, Lacchetti, Adkins, Anadkat, et al. (2021). Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *Journal of Clinical Oncology, 39*(36). doi: 10.1200/JCO.21.01440

Schneider, B.J et al. (2021). Management of immune-relatedadverse events in patients treated with checkpoint inhibitortherapy: ASCO Guideline update. Journal of Clinical Oncology, 39.4073-4126

U.S. Department of Health and Human Services, National Cancer Institute. (2017). *Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0*. NCI CTCAE v5.0

Vulsteke, Adra, Danchaivijitr, Sabadash et al. (2026). Perioperative enfortumab vedotin and pembrolizumab in bladder cancer. *The New England Journal of Medicine. Doi 10.1056/NEJMoa2511674*