

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

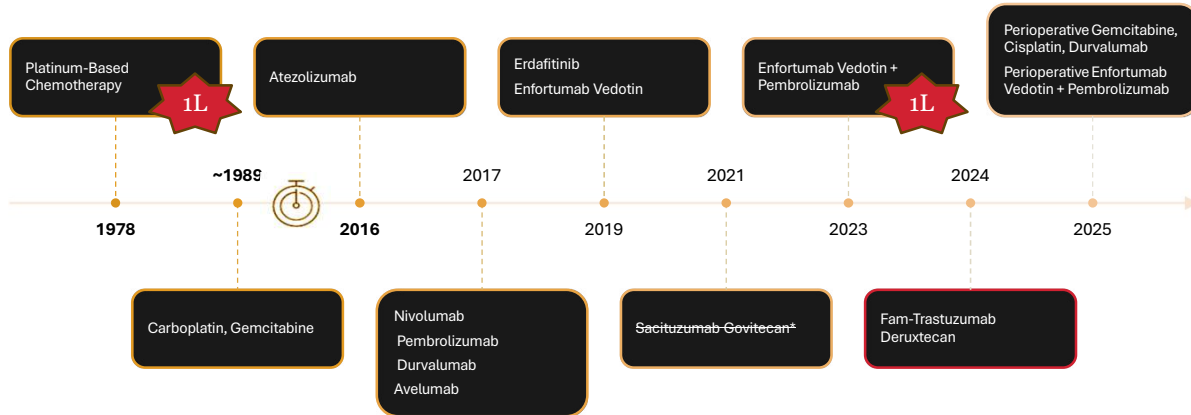
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Disclosures

- No relevant disclosures

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%

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- Sacituzumab govitecan (SG) — Withdrawn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-vnvc (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%)

Skin Toxicity

Peripheral
Neuropathy

Hyperglycemia

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.

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

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 trials
- **#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 (UNITE)
- 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.

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

Immune-Mediated Adverse Events

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

Conclusion

- Novel therapeutic agents = Novel toxicities
- Proactive monitoring, history solicitation, and early interventions are critical
- Dose modifications preserve efficacy while managing toxicity
- Team approach is best, use your multidisciplinary team
- Toxicities should not prevent use of this highly effective regimen, but dose reductions should not be scary either

Key Takeaways

- 01** Proactive monitoring, thorough history, and early intervention keep patients on therapy
- 02** Dose modifications preserve efficacy — dose reductions should NOT be feared
- 03** Use your multidisciplinary team: dermatology, neurology, endocrinology, ophthalmology, PT/OT
- 04** These toxicities should not prevent use of the most significant advance in bladder cancer treatment in decades
- 05** Accurate attribution (EV vs pembro vs combination) guides optimal management

Resources

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