
Antibody-Drug Conjugates in Bladder Cancer: Guideline Updates and Adverse Event Management
Jointly provided by
PACE
Partners for Advancing Clinical Education
BCAN
Bladder Cancer Advocacy Network
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Redefining Medical Education
Support for this activity has been provided through an educational grant from Astellas and Pfizer, Inc.

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Chapter 1: New and Emerging Role of ADCs in the Treatment of mUC and MIBC

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Clinical Case: Overview

- 67-year-old man with metastatic urothelial cancer (mUC)
  - Metastases to liver and bone
- Treated with enfortumab vedotin + pembrolizumab

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Enfortumab Vedotin + Pembrolizumab: *EV-302/KEYNOTE-A39 Study*

Patient population (N=886)

- Previously untreated locally advanced or mUC
- Eligible for platinum and EVP
- PD-L1 inhibitor naïve
- GFR ≥30 mL/min
- ECOG PS ≤2

Treatment

- Randomized 1:1 → EVP
  Gemcitabine + cisplatin/carboplatin
- Treatment until disease progression (per BICR), clinical progression, unacceptable toxicity, or completion of maximum cycles

End points

Dual primary end points

- PFS by BICR
- OS

Select secondary end points

- ORR per RECIST v1.1 by BICR and investigator assessment
- Safety

mUC, metastatic urothelial cancer; EVP, enfortumab vedotin + pembrolizumab; GFR, glomerular filtration rate; ECOG, Eastern Cooperative Oncology Group; BICR, blinded independent central review; PFS, progression-free survival; OS, overall survival; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors

Powles T et al. *N Engl J Med.* 2024;390:875.

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Enfortumab Vedotin + Pembrolizumab: *EV-302/KEYNOTE-A39 Study*

- EV-302/KEYNOTE-A39 showed superiority of EVP over chemotherapy
  - PFS = 12.5 months vs 6.3 months
  - OS = 31.5 months vs 16.1 months
  - ORR = 67.7% vs 44.4%
  - CR = 29.1% vs 12.5%

EVP, enfortumab vedotin + pembrolizumab; PFS, progression-free survival; OS, overall survival; ORR, overall response rate; CR, complete response

Powles T et al. *N Engl J Med.* 2024;390:875.
National Comprehensive Cancer Network Guidelines Bladder Cancer v6.2024.

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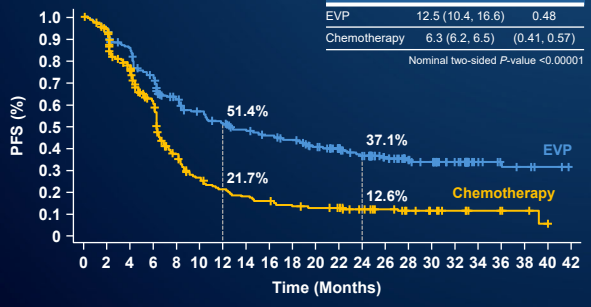
EV-302/KEYNOTE-A39 Study
PFS and OS Benefit Maintained With Longer Follow-Up

PFS by BICR in the Overall Population

PFS benefit with EVP was maintained with 1 additional year of follow-up

	Median PFS, mo (95% CI)	Stratified HR (95% CI)
EVP	12.5 (10.4, 16.6)	0.48
Chemotherapy	6.3 (6.2, 6.5)	(0.41, 0.57)

Nominal two-sided *P*-value <0.00001

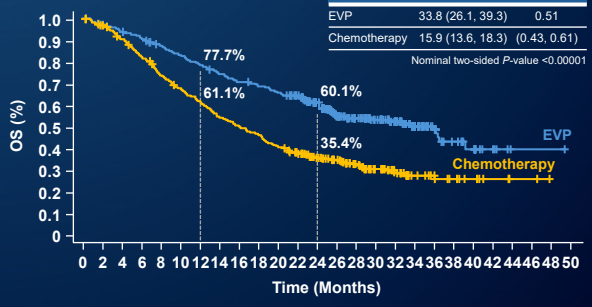


OS in the Overall Population

Risk of death was reduced by almost 50%

	Median OS, mo (95% CI)	Stratified HR (95% CI)
EVP	33.8 (26.1, 39.3)	0.51
Chemotherapy	15.9 (13.6, 18.3)	(0.43, 0.61)

Nominal two-sided *P*-value <0.00001



PFS, progression-free survival; OS, overall survival; BICR, blinded independent central review; EVP, enfortumab vedotin + pembrolizumab; CI, confidence interval; HR, hazard ratio

Powles T et al. *J Clin Oncol.* 2025;43. Abstract 664.

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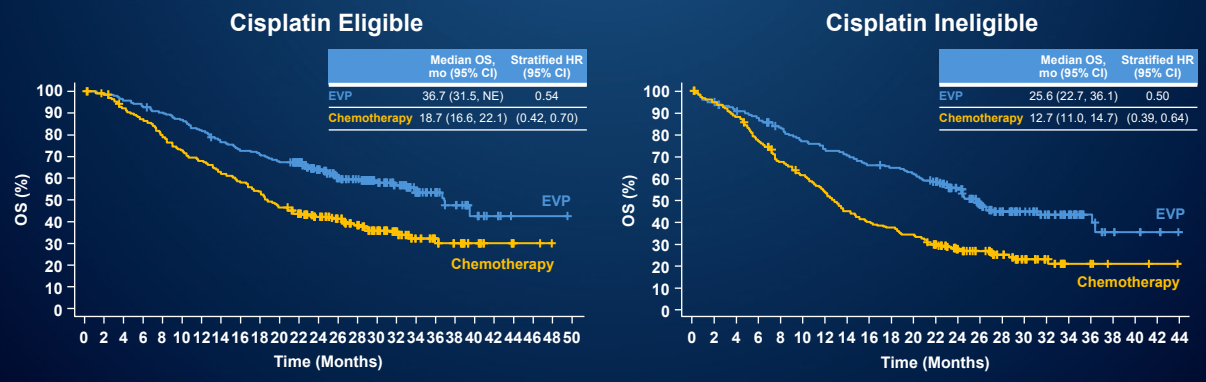
EV-302/KEYNOTE-A39 Study
Cisplatin Eligibility and PD-L1 Expression

OS Subgroup Analysis: Cisplatin Eligibility



OS benefit was consistent with the overall population, regardless of cisplatin eligibility

OS, overall survival; EVP, enfortumab vedotin + pembrolizumab; CI, confidence interval; NE, not estimable; HR, hazard ratio; CPS, combined positive score
Powles T et al. *J Clin Oncol*. 2025;43. Abstract 664.

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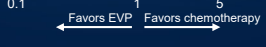
EV-302/KEYNOTE-A39 Study
PD-L1 Expression

	Median OS, months (event/N) EVP	Chemotherapy	HR (95% CI)
Overall	33.8 (203/442)	15.9 (297/444)	0.513 (0.428, 0.614)
Liver metastases			
Present	19.1 (68/100)	10.1 (82/99)	0.556 (0.399, 0.776)
Absent	39.9 (135/342)	18.3 (215/345)	0.496 (0.400, 0.615)
PD-L1 expression			
Low (CPS <10)	31.2 (91/184)	15.1 (136/185)	0.472 (0.361, 0.618)
High (CPS ≥10)	36.5 (111/254)	17.1 (158/254)	0.550 (0.431, 0.703)
Cisplatin eligibility			
Eligible	36.7 (101/244)	18.7 (143/234)	0.541 (0.419, 0.699)
Ineligible	25.6 (102/198)	12.7 (154/210)	0.498 (0.386, 0.642)
Metastatic disease site			
Visceral metastases	25.7 (163/318)	13.5 (235/318)	0.505 (0.412, 0.619)
Lymph node only	NR (34/103)	24.4 (54/104)	0.512 (0.332, 0.789)
Renal function			
Normal	39.3 (33/84)	18.6 (61/95)	0.496 (0.318, 0.773)
Mild	36.5 (69/165)	18.4 (101/162)	0.502 (0.365, 0.689)
Moderate/severe	25.6 (101/193)	13.3 (135/187)	0.528 (0.405, 0.689)



OS benefit was consistent with overall population, regardless of...
- ***PD-L1 expression status***

EVP, enfortumab vedotin + pembrolizumab; CI, confidence interval; HR, hazard ratio; OS, overall survival; CPS, combined positive score; NR, not reached
Powles T et al. *J Clin Oncol*. 2025;43. Abstract 664.

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EV-302/KEYNOTE-A39 Study

Liver Metastases and Metastatic Disease Site

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OS benefit was consistent with overall population, regardless of...

- ***Presence/absence of liver or visceral metastases***

EVP, enfortumab vedotin + pembrolizumab; CI, confidence interval; HR, hazard ratio; OS, overall survival; CPS, combined positive score; NR, not reached

Powles T et al. *J Clin Oncol*. 2025;43. Abstract 664.

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Clinical Case, Revisited

- 67-year-old man with mUC to liver and bone
- Treated with EVP
- Disease progression on EVP at first scan
- Gemcitabine/carboplatin ×5 cycles with partial response; poorly tolerated
- Palliative radiation, treatment break
- New biopsy

Biomarker	Method	Analyte	Result
ERBB2 (HER2/Neu)	IHC	Protein	Positive I 3+, 20%

mUC, metastatic urothelial cancer; EVP, enfortumab vedotin + pembrolizumab; IHC, immunohistochemistry

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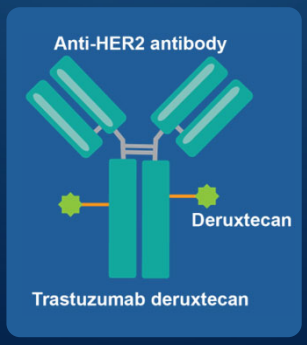
Trastuzumab Deruxtecan for Pretreated Patients With HER2-Expressing Solid Tumors

DESTINY-PanTumor02 Study

- Trastuzumab deruxtecan 5.4 mg/kg once every 3 weeks
  - Endometrial cancer
  - Bladder cancer
  - Other tumors
  - Cervical cancer
  - Biliary tract cancer
  - Ovarian cancer
  - Pancreatic cancer



Bladder cancer results

- 41 patients with HER2-expressing bladder cancer
  - IHC3+, n=16
  - IHC2+, n=20
- Prior therapies
  - 0, 1, or 2: 22 (54%)
  - >2: 19 (46%)
- Overall response rate
  - All: 39.0%
  - IHC3+: 56.3%
  - IHC2+: 35.0%

IHC, immunohistochemistry

Meric-Bernstam F et al. *J Clin Oncol*. 2023;42:47.

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Clinical Case, Revisited

- Trastuzumab deruxtecan initiated
- After 3 cycles, MRI report = “Previously seen hepatic lesions are no longer visualized, with residual scar”
- Stable bone metastases; no new sites of disease
- Patient now 20 months since diagnosis of metastatic disease, continuing on trastuzumab deruxtecan

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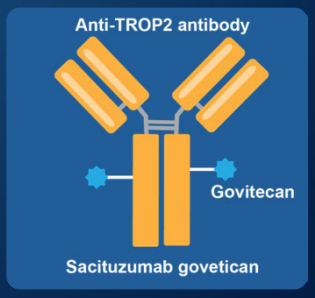
Sacituzumab Govitecan: *TROPHY-U01 Study*

Multicohort open-label phase 2 study in patients with mUC progressing after platinum-based chemotherapy and immune checkpoint inhibitors

	Prior Therapy	ORR	mPFS (mo)	mOS (mo)
Cohort 1 n=113	Post-platinum/ Post-CPI	28%	5.4	10.9



April 2021: FDA granted accelerated approval for SG for patients with locally advanced or metastatic urothelial cancer who previously received platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor contingent on verification of clinical benefit in confirmatory trial.

mUC, metastatic urothelial cancer; CPI, checkpoint inhibitor; ORR, overall response rate; mPFS, median progression-free survival; mOS, median overall survival; SG, sacituzumab govitecan

Loriot Y et al. *Annals Oncol*. 2024;35:392.

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Sacituzumab Govitecan: *TROPiCS-04 Study*

- Randomized phase 3 study of sacituzumab govitecan vs chemotherapy in pretreated advanced urothelial carcinoma
- Primary end point not met
- Neutropenia was a common adverse event

Median OS, months (95% CI)		Stratified hazard ratio (95% CI)	Stratified log-rank P value
SG (n=355)	TPC (n=356)		
10.3 (9.1-11.8)	9.0 (7.5-9.7)	0.86 (0.73-1.02)	0.087

Sacituzumab govitecan withdrawn from US market in November 2024.

SG, sacituzumab govitecan; TPC, treatment of physician's choice; OS, overall survival; CI, confidence interval

Powles T el al. *Annals Oncol*. 2025. Epub ahead of print.

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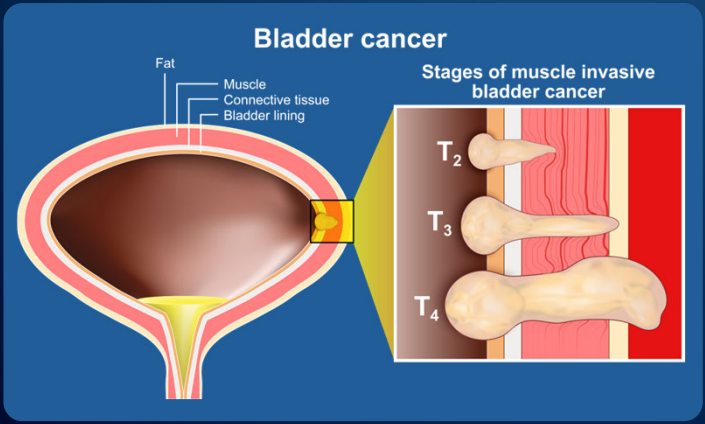
Muscle-Invasive Bladder Cancer



Neoadjuvant therapy SOC

Preferred therapy

- Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC)

Other recommended regimens

- Gemcitabine and cisplatin

SOC, standard of care
National Comprehensive Cancer Network Guidelines Bladder Cancer v6.2024.

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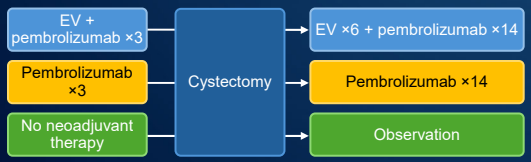
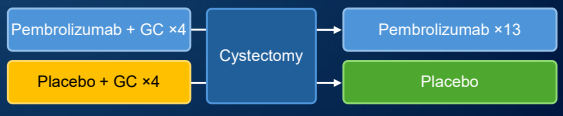
Current MIBC Perioperative Trials

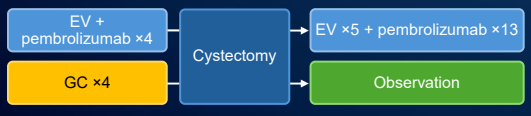
KEYNOTE-905/EV-303



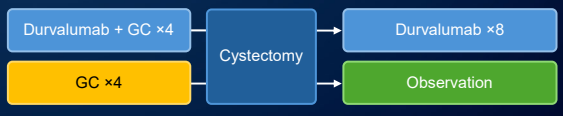
KEYNOTE-866



KEYNOTE-B15/EV-304



NIAGARA



MIBC, muscle-invasive bladder cancer; EV, enfortumab vedotin; GC, gemcitabine + cisplatin; NAC, neoadjuvant chemotherapy
Necchi A et al. *J Clin Oncol*. 2023;41. Abstract TPS585. Galsky MD et al. *Future Oncol*. 2021;17:3137. Powles TB et al. *Annals Oncol*. 2024;35. Abstract S1271. Hoimes CJ et al. *J Clin Oncol*. 2021;39. Abstract TPS4587.

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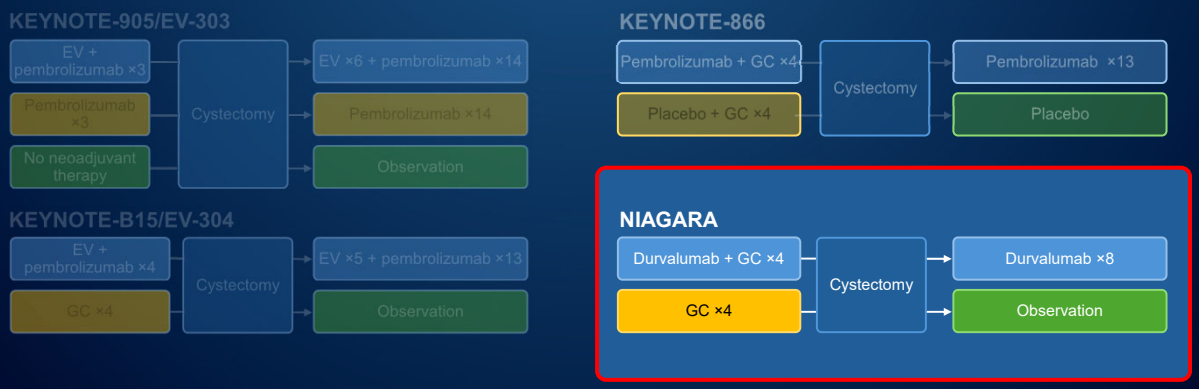
Current MIBC Perioperative Trials



MIBC, muscle-invasive bladder cancer; GC, gemcitabine + cisplatin

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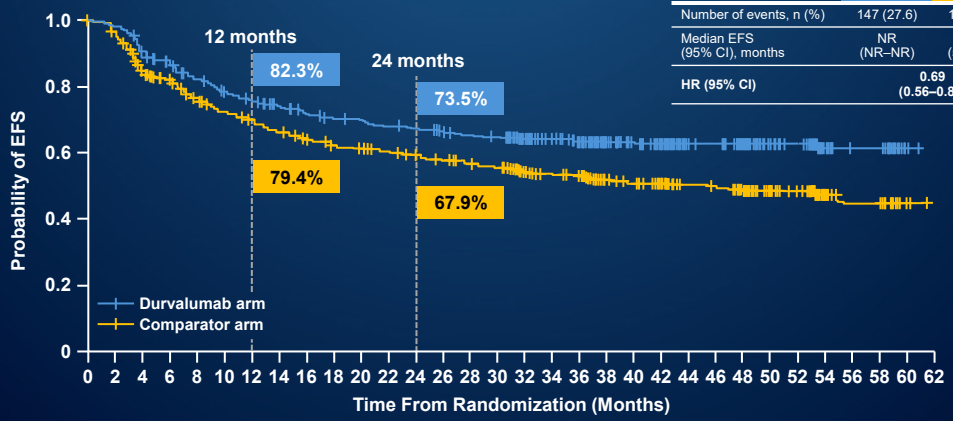
NIAGARA Study
Event-Free Survival

Patients Who Did Not Undergo RC Were Censored



	Durvalumab arm N=533	Comparator arm N=530
Number of events, n (%)	147 (27.6)	186 (35.1)
Median EFS (95% CI), months	NR (NR–NR)	NR (53.2–NR)
HR (95% CI)	0.69 (0.56–0.86)	

EFS was assessed using RECIST v1.1. EFS is defined as the time from randomization to the first: (1) progressive disease that precluded RC; (2) recurrence after RC; (3) date of expected surgery in patients who did not undergo RC; (4) death from any cause. Data cutoff 29 Apr, 2024.

CI, confidence interval; EFS, event-free survival; HR, hazard ratio; ITT, intent-to-treat population; NR, not reached; RC, radical cystectomy; RECIST, Response Evaluation Criteria In Solid Tumors

Powles TB et al. *Annals Oncol*. 2024;35. Abstract S1271.

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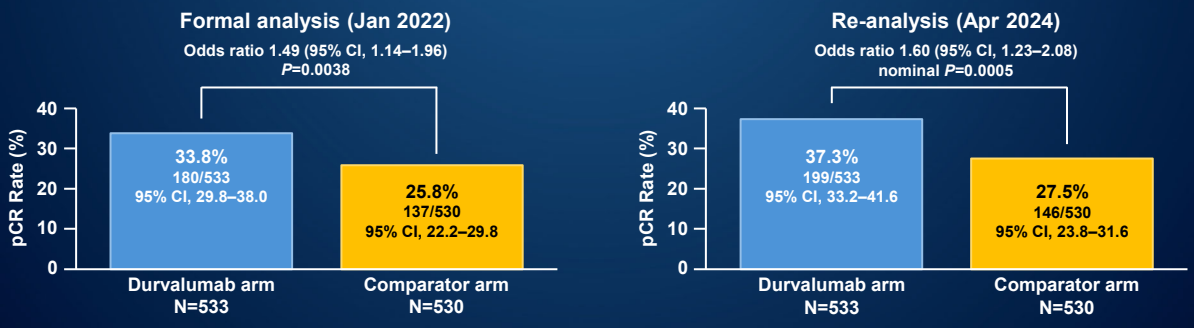
NIAGARA Study
Pathologic Complete Response



- The planned formal analysis for pCR was not statistically significant (threshold for significance, *P*=0.001)
- 59 evaluable samples were incorrectly considered nonresponders rather than their true result

- The re-analysis showed nominal statistical significance in favor of the durvalumab arm
- This analysis includes the results of the 59 omitted samples (28 additional pCRs)

CI, confidence interval; DCO, data cutoff; ITT, intent-to-treat population; pCR, pathologic complete response; RC, radical cystectomy
Powles TB et al. *Annals Oncol.* 2024;35. Abstract S1271.

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Chapter 2: Managing AEs Caused by ADCs in Patients With mUC

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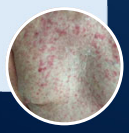
Enfortumab Vedotin + Pembrolizumab
AEs of Clinical Interest

Skin reactions

- Seen with both EV and pembrolizumab but more frequently with combination (EVP)
- 70% of patients treated with EVP
- Onset typically within 1-2 months
- Erythematous and scaly
- Pruritic papules
- Interiginous, flexural, and possible truncal



Hyperglycemia/ diabetes mellitus

- Seen with both EV and pembrolizumab but more commonly with EV
- 13% of patients treated with EVP
- Early onset, typically 2 weeks
- Mechanism unknown
- Likely insulin resistance
- Risk: high BMI and A1c >6.5%

Peripheral neuropathy

- Anticipated AE with ADCs, rarely with pembrolizumab
- Second most common AE: 67% of patients treated with EVP
- Most frequent reason for EV discontinuation
- Onset generally occurs later (median onset: 6 months)

AE; adverse event; EV, enfortumab vedotin; EVP, enfortumab vedotin + pembrolizumab
Brower B et al. *Front Oncol*. 2024;14:1326715.

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Enfortumab Vedotin + Pembrolizumab
AEs of Clinical Interest

Pneumonitis

- Seen with both EV and pembrolizumab
- Includes severe, life-threatening, or fatal events
- Occurred in 10% of patients treated with EVP
- Median onset is 4 months

Gastrointestinal

- Includes diarrhea, constipation, nausea, and dysgeusia
- Seen in 21% to 38% of patients treated with EVP
- Most events were mild

Fatigue

- Common in cancer patients
- 51% of patients treated with EVP experienced fatigue

Ocular

- Commonly seen with EV
- Dry eye was most common, seen in 24% of patient treated with EVP
- Generally mild

AE; adverse event; EV, enfortumab vedotin; EVP, enfortumab vedotin + pembrolizumab
Brower B et al. *Front Oncol*. 2024;14:1326715.

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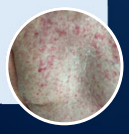
Enfortumab Vedotin + Pembrolizumab *AE Management*

Skin reactions

- Remind patient to report rash and use sunscreen
- Careful skin exam, rule out mucosal involvement/Steven Johnson syndrome
- Topical steroid cream
- Hydroxyzine for itch
- EV dose hold/dose reduction
- Systemic steroids and/or dermatology referral for refractory/extensive cases

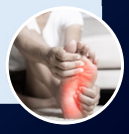


Hyperglycemia/ diabetes mellitus

- Optimize glycemic control in patients with diabetes. Involve endocrinology
- Check glucose prior to each infusion
- Hold EV is glucose >250
- If severe, consider steroids as could be T1DM from pembrolizumab

Peripheral neuropathy

- Baseline assessment for existing neuropathy
- Ask about neuropathy at visits
- Ensure gait is not affected
- Dose hold/dose reduction/ schedule extension
- Discontinue EV if excellent response and/or neuropathy is interfering with ADLs
- Adjunctive therapy for neuropathic pain (gabapentin, pregabalin, duloxetine)



AE; adverse event; EV, enfortumab vedotin; T1DM, type 1 diabetes mellitus; ADL, activities of daily living
Brower B et al. *Front Oncol*. 2024;14:1326715.

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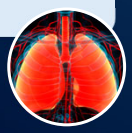
Enfortumab Vedotin + Pembrolizumab *AE Management*

Pneumonitis

- No symptoms: hold EV, restart at lower dose
- Mild symptoms: oral steroids, slow taper, restart at lower dose
- Severe symptoms: high-dose steroids, discontinue permanently



Gastrointestinal

- Management ranges from medications for symptom management to holding or discontinuing both agents, depending on severity

Fatigue

- Management includes lifestyle changes, medications, and dose interruption/modification

Ocular

- Management includes prompt referral to ophthalmologist, dose interruption, and medications to manage symptoms

AE; adverse event; EV, enfortumab vedotin
Brower B et al. *Front Oncol*. 2024;14:1326715.

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Trastuzumab Deruxtecan
Management of AEs of Clinical Interest

	Before T-DXd	Infusion	Days 2–4	Days 5–21	Post-T-DXd treatment
Nausea and vomiting	• 1st cycle (and subsequent cycles if adequate): 5-HT_3 RA + DEX • If inadequate: NK1 RA + 5-HT_3 RA + DEX ± olanzapine		• 1st cycle: DEX ± metoclopramide or 5-HT_3 RA • If inadequate: NK1 RA + 5-HT_3 RA ± DEX or DEX ± metoclopramide ± olanzapine	• Delayed onset: olanzapine or metoclopramide ± DEX	
Neutropenia	• Prophylaxis with G-CSF for patients with prior neutropenic complications, but do not give routinely to patients with afebrile neutropenia		• Grade 3: Interrupt T-DXd until resolved to grade ≤2 then maintain dose • Grade 4: Interrupt T-DXd until resolved to grade ≤2 then reduce dose by 1 dose level		
Infusion-related reactions	• Collect medical history (i.e. allergic disorders, atopic status, and concomitant treatments) • Prophylaxis with ranitidine (150 mg p.o.), diphenhydramine (50 mg p.o.), chlorpheniramine (10 mg p.o.), or pantoprazole (40 mg p.o.); may also include DEX (4–8 mg p.o.) or hydrocortisone injections (125 or 250 mg)	• First infusion, 90 min; if tolerated, subsequent infusions can be 30 min • For grade 1 or 2, reduce rate 50% or stop • If anaphylaxis is suspected, follow local guidelines [may include epinephrine (1 mg/ml i.m. every 5-15 min), normal saline (1–2 l i.v. at 5-10 ml/kg for the first 5 min), and H1/H2 antagonists]			
Alopecia	• Initiate scalp cooling 20–45 min before infusion	• Continue scalp cooling until 20—50 min after infusion			• Consider bimatoprost or minoxidil once treatment has ended to help with regrowth
Fatigue	• Complete full assessment (clinical history, symptoms, etc.)		• Follow specified treatment guidelines if treatable factor is found • Educate patient and caregiver on ways to properly manage fatigue • Encourage physical activity and psychosocial interventions • Consider short-term pharmacological interventions in patients with metastatic cancer		

AE, adverse event; 5-HT_3, serotonin type 3; DEX, dexamethasone; G-CSF, granulocyte colony-stimulating factor; ILD, interstitial lung disease; i.m., intramuscular; i.v., intravenous; LVEF, left ventricular ejection fraction; NK1, neurokinin-1; p.o., by mouth; RA, receptor antagonist; T-DXd, trastuzumab deruxtecan

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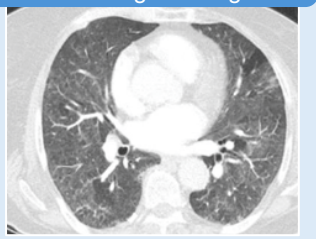
Trastuzumab Deruxtecan
Interstitial Lung Disease/Pneumonitis Management

Radiologic findings



Symptoms
- Hypoxia
- Cough
- Dyspnea

Interstitial lung disease: 10% of patients treated with trastuzumab deruxtecan → **No symptoms**: Hold, restart
Symptoms: steroids, discontinue permanently

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To receive credit, complete
the posttest and evaluation.