Genitourinary Masterclass

Monitoring and warning signs for key AESIs

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EV as first-line therapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer. Combination therapy with pembrolizumab.

EV as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 or programmed death-ligand 1 inhibitor, and have received a platinum-containing chemotherapy

1L, first line; EV, enfortumab vedotin; P, pembrolizumab; PADCEV® (enfortumab vedotin). Prescribing Information July 2025 | MAT-KR-PAD-2025-00074

PADCEV®
enfortumab vedotin
Injection for IV infusion 20 mg & 30 mg vials

astellas

Disclaimers

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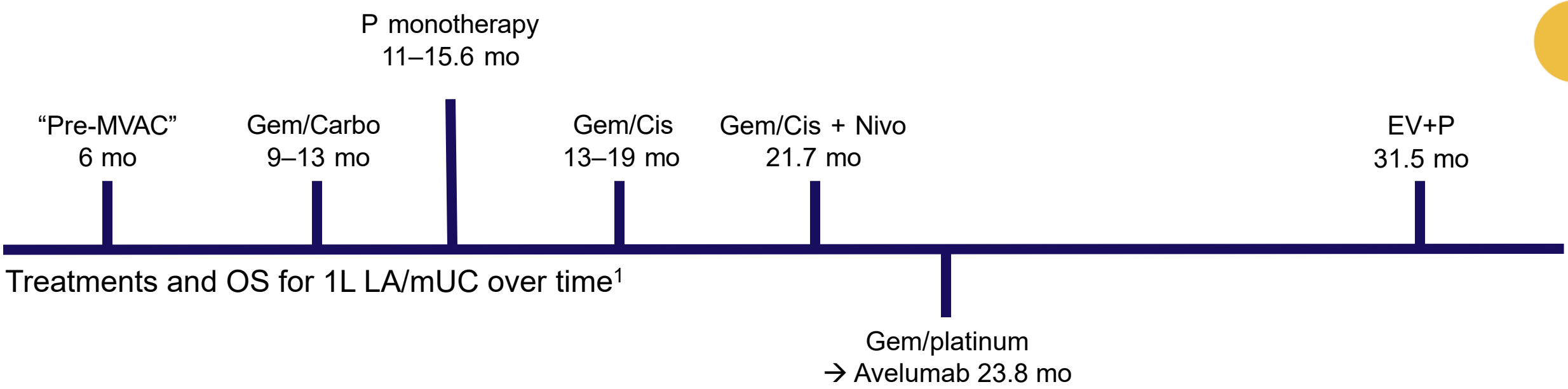
The LA/mUC treatment landscape has evolved over time[1]



While the efficacy data for EV+P is compelling, careful patient monitoring and TRAE mitigation is crucial to ensure patients can benefit from optimal outcomes[2,3]

Patient and disease characteristics that should be taken into consideration include disease pace, symptoms, performance status, comorbidities (renal function, pre-existing neuropathy, diabetes, BMI, lung disease, autoimmune disease), distance from the treatment center, and patient goals for care[2,4]

Disclaimer: EV+P may not be approved in your region. This content is shared to support proactive AE management of EV (as monotherapy or in combination), not to highlight efficacy. Please refer to local guidelines for appropriate use.

AE, adverse event; BMI, body-mass index; Cis, cisplatin; Carbo, carboplatin; EV, enfortumab vedotin; Gem, gemcitabine; LA/mUC, locally advanced/metastatic urothelial carcinoma; mo, months; MVAC, Methotrexate, vinblastine, doxorubicin + cisplatin; Nivo, nivolumab; OS, overall survival; P, pembrolizumab; TRAE, treatment-related adverse event.

1. O'Donnell P, et al. Presented at ASCO GU 2024; 2. Speakers expert opinion; 3. Brower B et al. *Front Oncol* 2024;14:1326715; 4. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

AE occurrence with EV vs. PBCT in the EV-301 trial

TRAEs, n (%)*	EV group (n=296)†		Chemotherapy group (n=291)†	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	278 (93.9)	155 (52.4)	267 (91.8)	147 (50.5)
Alopecia	135 (45.6)	NR	108 (37.1)	NR
Peripheral sensory neuropathy	103 (34.8)	15 (5.1)	63 (21.6)	6 (2.1)
Pruritus	96 (32.4)	4 (1.4)	14 (4.8)	1 (0.3)
Fatigue	93 (31.4)	20 (6.8)	66 (22.7)	13 (4.5)
Decreased appetite	92 (31.1)	9 (3.0)	69 (23.7)	5 (1.7)
Diarrhea	74 (25.0)	10 (3.4)	49 (16.8)	5 (1.7)
Dysgeusia	73 (24.7)	NR	22 (7.6)	NR
Nausea	71 (24.0)	3 (1.0)	64 (22.0)	4 (1.4)
Maculopapular rash	50 (16.9)	22 (7.4)	5 (1.7)	0
Anemia	34 (11.5)	8 (2.7)	63 (21.6)	23 (7.9)
Decreased neutrophil count	31 (10.5)	18 (6.1)	51 (17.5)	41 (14.1)
Neutropenia	20 (6.8)	14 (4.7)	25 (8.6)	18 (6.2)
Decreased white-cell count	15 (5.1)	4 (1.4)	32 (11.0)	21 (7.2)
Febrile neutropenia	2 (0.7)	2 (0.7)	16 (5.5)	16 (5.5)

Disclaimer: PADCEV (enfortumab vedotin) can cause severe skin reactions, including SJS and TEN (predominantly during the first cycle of treatment).
*Occurring in ≥20% of patients in either treatment group or Grade ≥3 TRAEs occurring in ≥5% of patients in either treatment group; †Safety population.
AE, adverse event; EV, enfortumab vedotin; NR not reported; PBCT, platinum-based chemotherapy; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; TRAE, treatment-related adverse event.
Rosenberg JE et al. *Ann Oncol* 2023;13:1047–1054.

AE occurrence with EV+P vs. PBCT in the EV-302 trial

TRAE occurrence, %[1]	EV+P (n=440)		PBCT (n=433)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Overall	97.0	55.9	95.6	69.5
Any AE	97.0	55.9	95.6	69.5
Peripheral sensory neuropathy	50.0	3.6	9.9	0
Pruritus	39.8	1.1	4.8	0
Alopecia	33.2	0.5	7.9	0.2
Maculopapular rash	32.7	7.7	3.2	0
Fatigue	29.3	3.0	36.0	4.2
Diarrhea	27.5	3.6	11.1	0.7
Decreased appetite	26.8	1.1	22.6	1.4
Nausea	20.2	1.1	38.8	1.1
Anemia	13.9	3.4	56.6	31.4
Hyperglycemia	10.9	5.0	0.7	0
Neutropenia	9.1	4.8	41.6	30.0
Neutrophil count decreased	3.6	2.5	12.5	9.0
Thrombocytopenia	3.4	0.5	34.2	19.4
Platelet count decreased	0.7	0	14.5	6.5

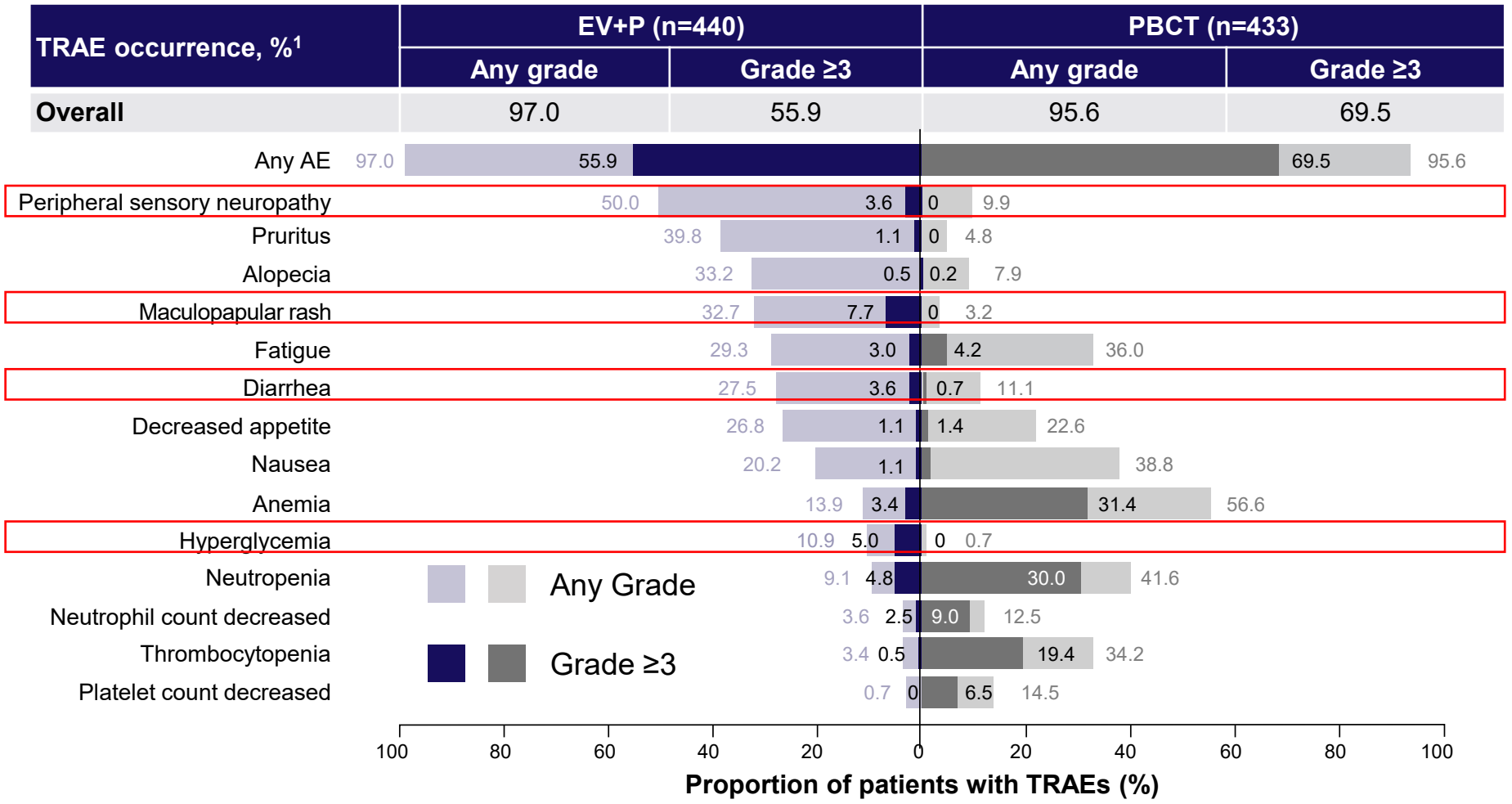


Figure adapted from Powles T et al. *N Engl J Med* 2024;390:875–888.

Serious TRAEs, n (%):[2]
- EV+P: 122 (27.7)
- PBCT: 85 (19.6)

TRAEs leading to death per investigator with:
EV+P, n=4 (0.9%):[1,2]
- Asthenia
- Diarrhea
- Immune-mediated lung disease
- Multiple organ dysfunction syndrome

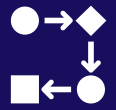
PBCT, n=4 (0.9%):[1,2]
- Febrile neutropenia
- Myocardial infarction
- Neutropenic sepsis
- Sepsis

TRAEs shown in the figure are any grade by preferred term in ≥20% of patients in either arm; Grade ≥3 TRAEs shown occurred in ≥5% of the patients in either treatment group.[1]
AE, adverse event; EV, enfortumab vedotin; P, pembrolizumab; PBCT, platinum-based chemotherapy; TRAE, treatment-related adverse event.
1. Powles T et al. *N Engl J Med* 2024;390:875–888; 2. Powles T et al. *N Engl J Med* 2024;390:875–888 (supplementary material).

Example patient scenarios requiring careful consideration

68-year-old treated with prior CisGem 2 years ago (achieved CR), with residual neuropathy Grade ~1/2, now with recurrent disease to several pelvic and inguinal nodes

61-year-old with DM, BMI of 32, HgBA1C = 7.9% and random Glu=190 mg/dL , not reliable with metformin, with metastatic disease to LN and lung

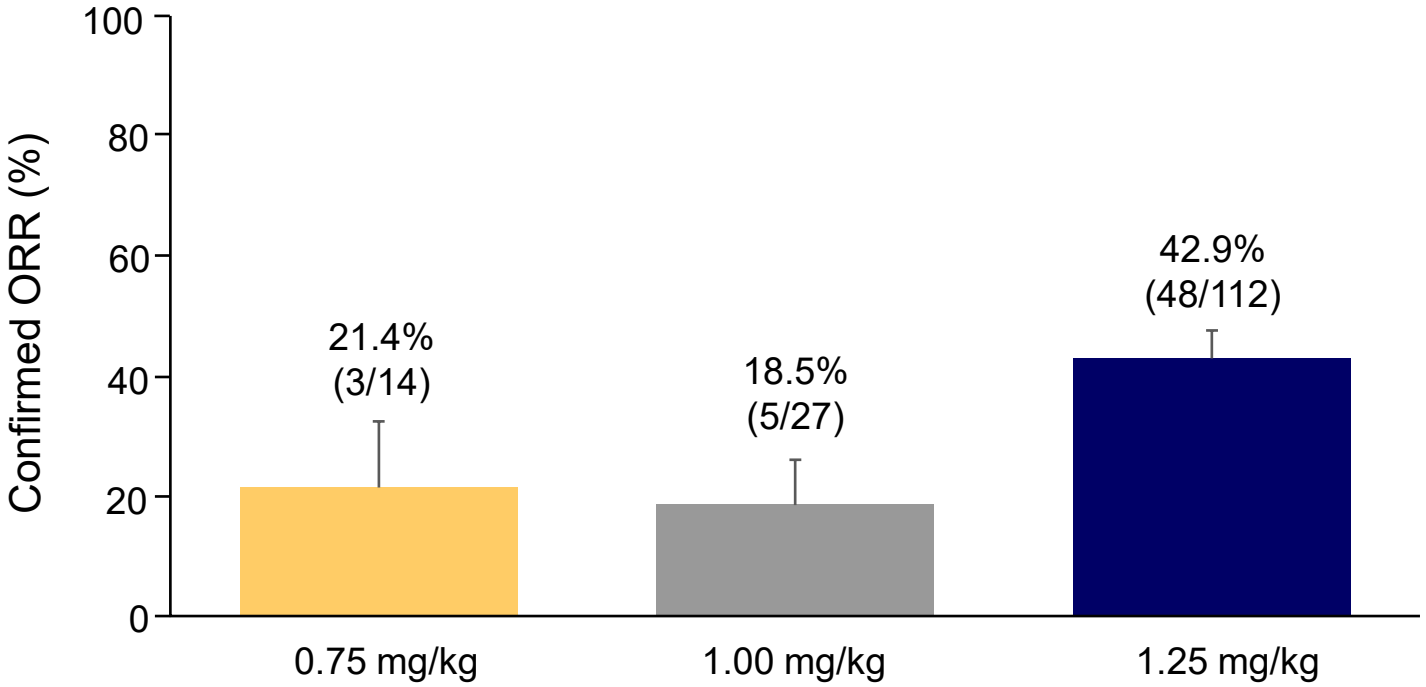


73-year-old with prior pT3N0 disease at cystectomy, treated with adjuvant nivolumab but develops newly metastatic disease 9 months into therapy

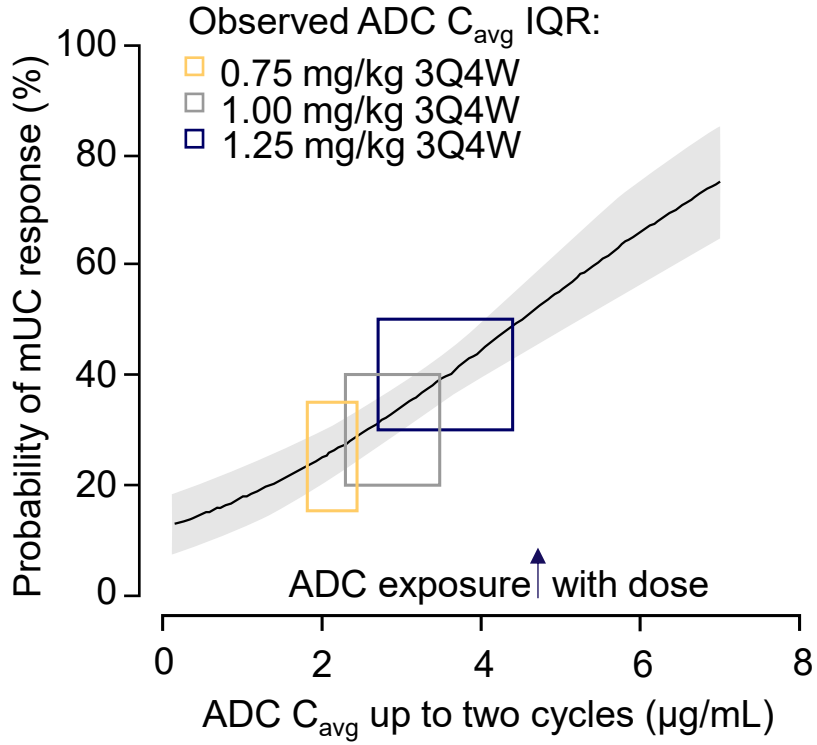
BMI, body mass index; CisGem, cisplatin-gemcitabine; CR, complete response; DM, diabetes mellitus; Glu, glucose; HgBA1C, hemoglobin A1c; LN, lymph node.
Slide provided courtesy of Dr Peter H O'Donnell.

In the Phase I EV-101 study, EV 1.25 mg/kg 3Q4W achieved the highest response rate of the three doses studied and was supported by exposure–response analysis

EV-101: ORR by EV starting dose



EV-101: Exposure–response for EV starting dose



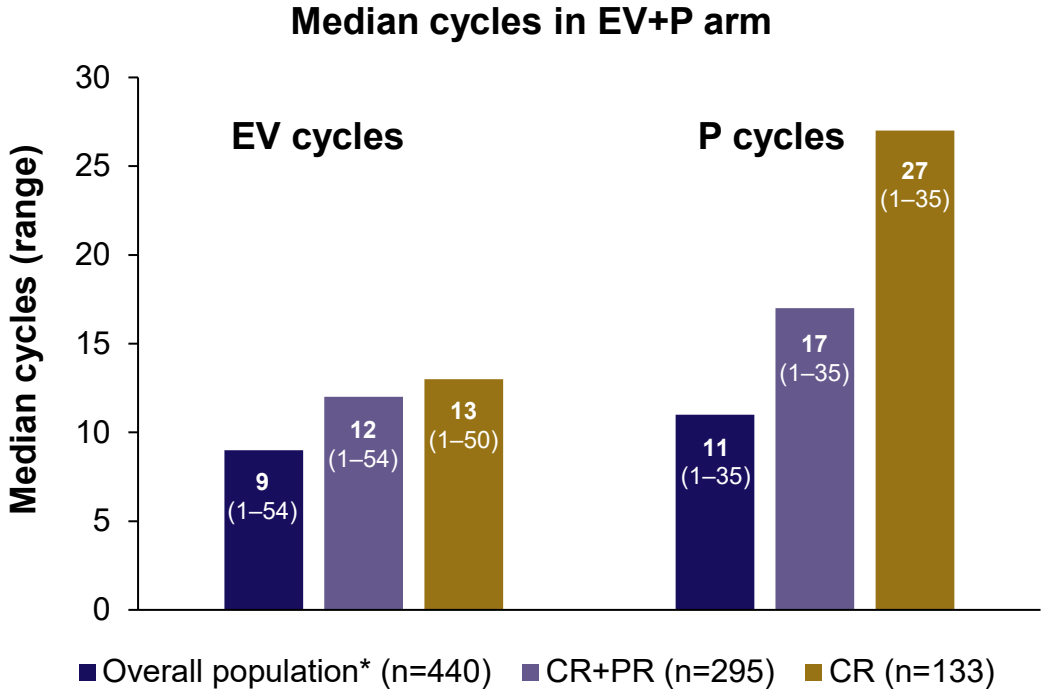
Disclaimer: For licensed starting dose information and information on dose adjustments please refer to local guidance.

Error bar = 1 standard deviation. Analysis populations for both dose–response and exposure–response were based on actual treatment arms.

3Q4W, Days 1, 8, and 15 of a 28-day cycle; ADC, antibody–drug conjugate; C_{avg}, time-averaged exposure; EV, enfortumab vedotin; IQR, interquartile range; mUC, metastatic urothelial carcinoma; ORR, objective response rate.

Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

Safety summary of responders vs. the overall population from EV-302



Safety summary

Patients with TRAE, n (%)	Overall population (safety analysis set)		Responders (CR+PR)		Patients with CR	
	EV+P (n=440)	PBCT (n=433)	EV+P (n=295)	PBCT (n=195)	EV+P (n=133)	PBCT (n=64)
All grades	428 (97.3)	414 (95.6)	293 (99.3)	189 (96.9)	133 (100.0)	62 (96.9)
Grade ≥3	252 (57.3)	301 (69.5)	181 (61.4)	129 (61.4)	82 (61.7)	46 (71.9)

- In the overall population,* EV+P treatment was given for a median of 12 cycles (range 1–54)
- For responders (CR+PR), EV+P treatment duration was longer (median number of cycles was 19 [range 1–54]), and among patients with CR, EV+P was given for a median of 30 cycles (range 1–50)
- A longer treatment duration was observed in responders (CR+PR or CR), with consistent safety profile

Disclaimer: EV+P may not be approved in your region. This content is shared to support proactive AE management of EV (as monotherapy or in combination), not to highlight efficacy. Please refer to local guidelines for appropriate use.

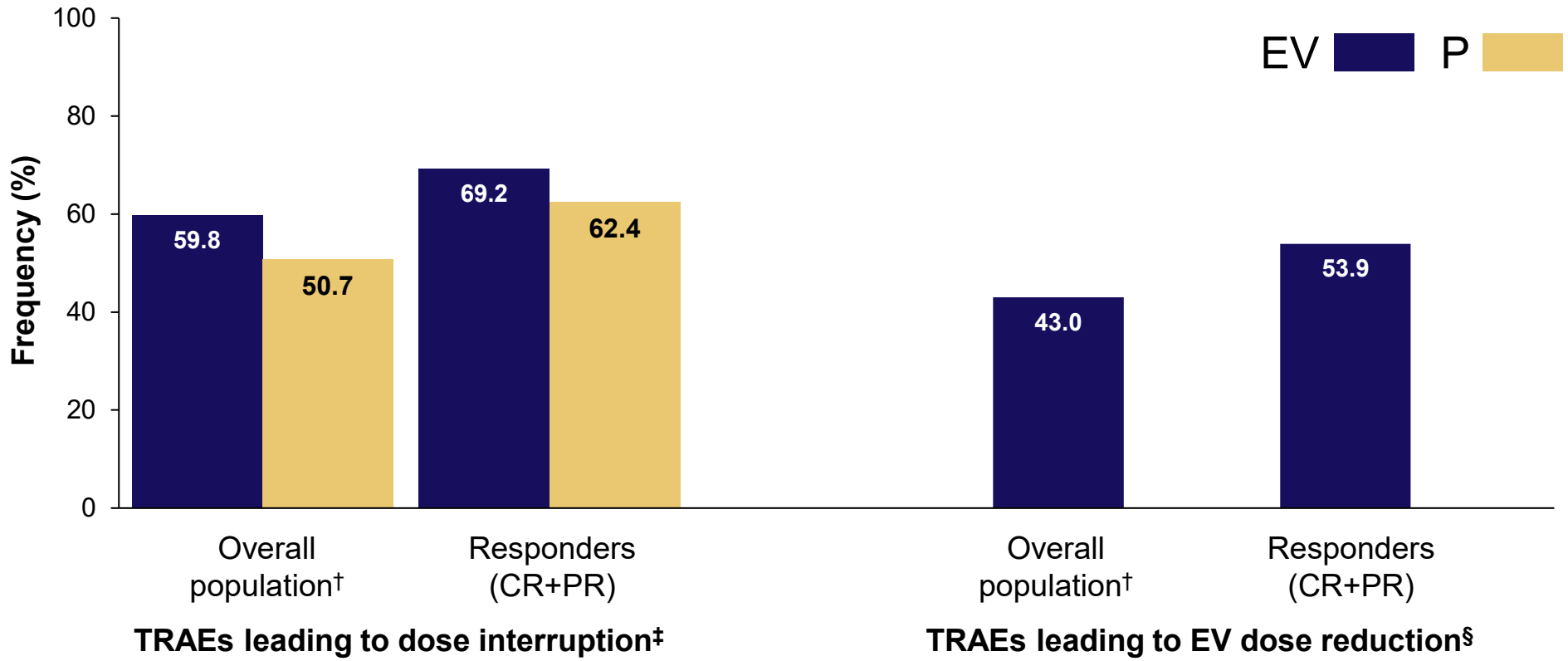
Data cutoff: August 8, 2024.

*Overall population refers to evaluable patients in the safety analysis set.

AE, adverse event; CR, complete response; EV, enfortumab vedotin; P, pembrolizumab; PBCT, platinum-based chemotherapy; PR, partial response; TRAE, treatment-related adverse event.

Gupta S et al. Presented at ASCO 2025. Abstract 4502.

In the EV+P arm of EV-302, dose modifications due to TRAEs* were common among responders (CR+PR) with longer treatment duration



Disclaimer: EV+P may not be approved in your region. This content is shared to support proactive AE management of EV (as monotherapy or in combination), not to highlight efficacy. Please refer to local guidelines for appropriate use.

Data cutoff: August 8, 2024. NCT04223856.

*TRAEs leading to discontinuation of EV occurred in 36.4% overall and 46.8% of responders. TRAEs leading to discontinuation of P occurred in 24.8% overall and 27.8% of responders; †Overall population refers to evaluable patients in the safety analysis set; ‡Dose interruption includes dose elimination (scheduled dose being skipped) and dose delay (dose not occurring on the scheduled dosing day) as collected on the case report form; §No dose reduction was permitted for P.

AE, adverse event; CR, complete response; EV, enfortumab vedotin; P, pembrolizumab; PR, partial response; TRAE, treatment-related adverse event.

Gupta S et al. Presented at ASCO 2025. Abstract 4502.

Real-world EV ± P treatment toxicity and dose modifications

Toxicity	n (%) of total	Median months to occurrence (range)	Dose held n (%)	Dose reduction n (%)	Discontinuation n (%)	Hospitalization n (%)
Skin reaction	74 (60)	0.7 (0.1–13.8)	33 (46)	33 (46)	4 (5)	4 (5)
Neuropathy	58 (47)	2.9 (0.2–9.6)	28 (48)	23 (40)	11 (20)	0 (0)
Ocular disorder	35 (28)	1.8 (0.2–10.6)	4 (11)	3 (9)	1 (3)	0 (0)
Hyperglycemia	17 (14)	1.4 (0.1–5.6)	5 (29)	0 (0)	0 (0)	0 (0)
Pneumonitis	3 (2)	3.8 (3.0–11.0)	1 (33)	0 (0)	0 (0)	1 (33)

- Retrospective cohort study of EV ± P initiators at the University of Pennsylvania (treatment initiation date 1/2020 – 5/2024; N=123)
- Treatment toxicity occurred in most patients, but discontinuation was infrequent

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The information presented in this slide has not been validated through pivotal or large-scale studies. Data are included here as part of the speaker's personal scientific opinion.
AE, adverse event; EV, enfortumab vedotin; P, pembrolizumab; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.
Kurian M, et al. Presented at ASCO 2025. Abstract 4562.

It is important we understand the safety profile of EV+P to stay ahead of AESIs

Skin toxicities[1,2]

Incidence: 70%
Grade ≥3: 17%

Severe skin reactions:[1]

1.7 months

Range: 0.1–17.2 months

Peripheral neuropathy[1–3]

Incidence: 63.2%
Grade ≥3: 6.8%

Grade ≥2:[3]

6 months

Range: 0.3–25 months

EV-302 trial exclusion criteria:[4]

Ongoing sensory or motor neuropathy Grade ≥2

Hyperglycemia[1–3]

Incidence: 13.0%
Grade ≥3: 8.9%

Any grade:[3]

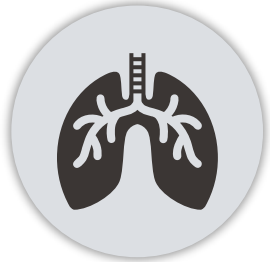
0.5 months

Range: 0.3–3.5 months

EV-302 trial exclusion criteria:[4]

Uncontrolled diabetes, defined as HbA_{1c} ≥8% or HbA_{1c} 7% to <8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained

Pneumonitis/ILD[1,2]



Incidence: 10.3%
Grade ≥3: 3.5%*

Any grade:[1]

4 months

Range: 0.3–26.2 months

EV-302 trial exclusion criteria:[4]

History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis

Ocular AEs[1–3]

Incidence: 21.4%

EV-302 trial exclusion criteria:[4]

Active keratitis or corneal ulcerations

Median time to onset

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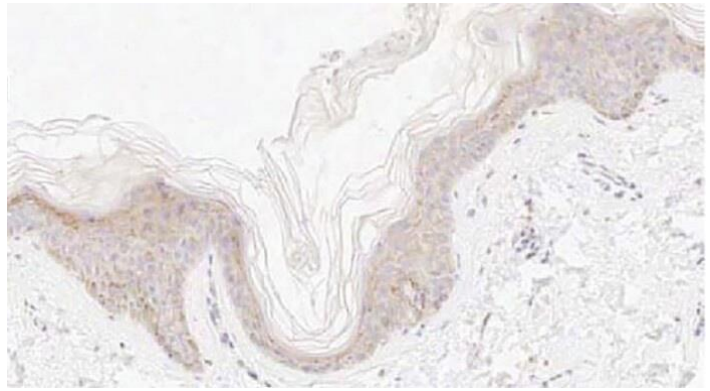
AE, adverse event; AESI, adverse event of special interest; EV, enfortumab vedotin; HbA_{1c}, glycated hemoglobin; ILD, interstitial lung disease; P, pembrolizumab; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

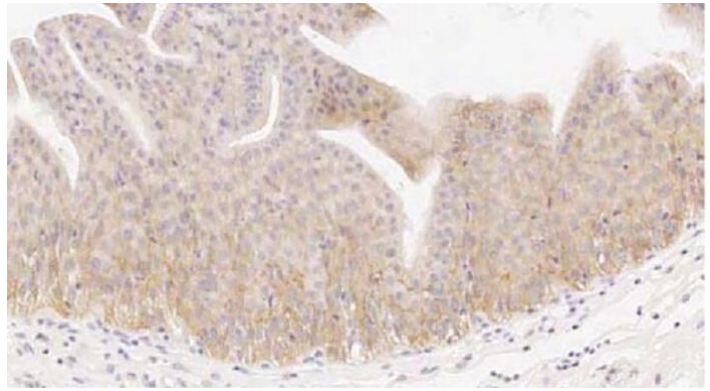
1. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 2. KEYTRUDA® (pembrolizumab). Summary of Product Characteristics; 3. Brower B et al. *Front Oncol* 2024;14:1326715;
4. Powles T et al. *N Engl J Med* 2024;390:875–888 (protocol).

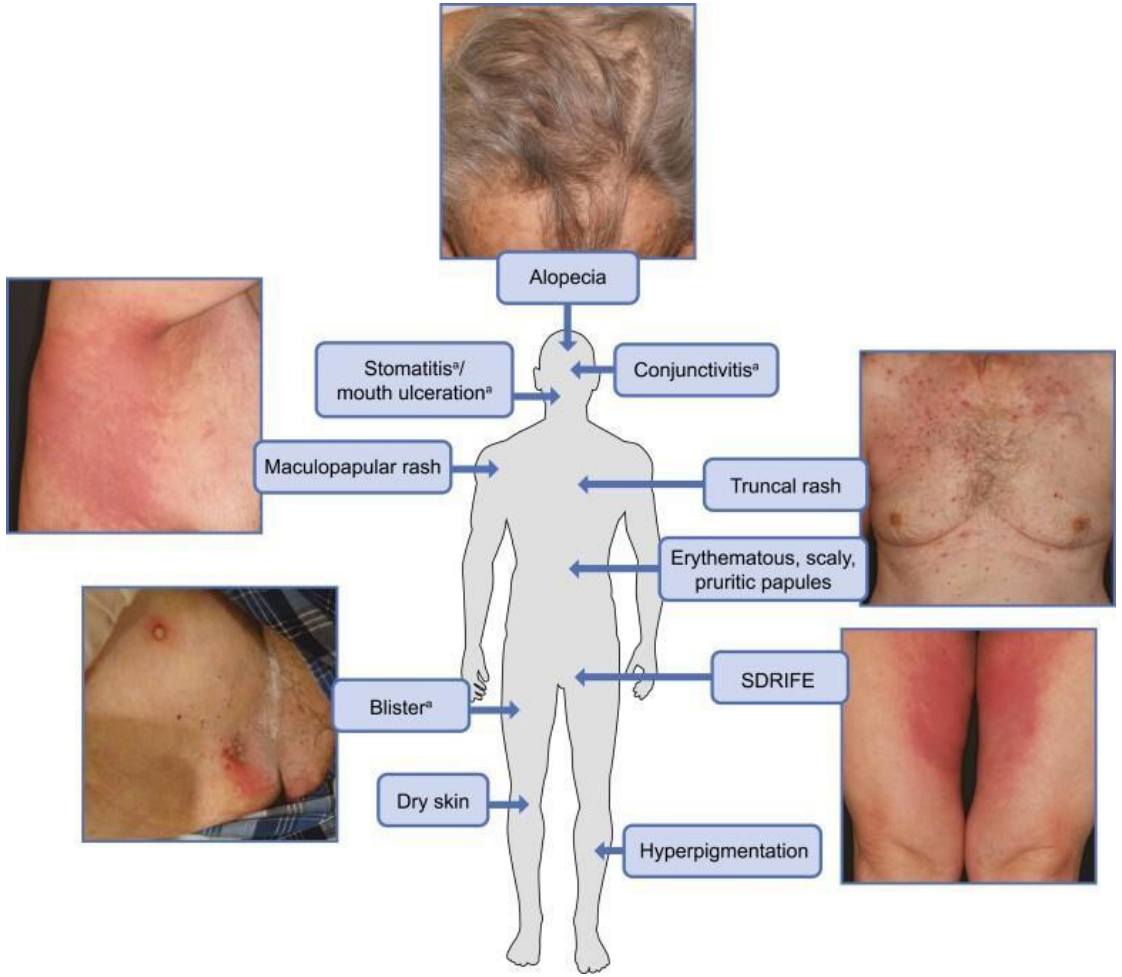
Cutaneous toxicities associated with EV may vary in morphology, distribution, and associated symptoms

Nectin-4 positive staining in skin*



Nectin-4 positive staining in bladder*





Images reproduced from 'Management of Dermatologic Events Associated With the Nectin-4-directed Antibody-Drug Conjugate Enfortumab Vedotin' Lacouture ME et al. *Oncologist* 2022;27:e223–e232. Available at: https://academic.oup.com/oncolo/article/27/3/e223/6537593?login=false. By CC: https://creativecommons.org/licenses/by-nc/4.0/

*Positive Nectin-4 staining (brown) by immunohistochemistry. EV, enfortumab vedotin; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema.

Lacouture ME et al. *Oncologist* 2022;27:e223–e232.

Skin toxicities: Risk factors and monitoring

Median time to onset of severe skin reactions:[3]

1.7 months

Most skin-related AEs are mild, transient, and occur early; however, they should still be reported and managed quickly to reduce the risk of progression to a more severe reaction, which may lead to EV+P treatment delays or discontinuation or even be fatal[1–3]

General risk factors for skin reactions to anti-cancer therapy[1,4]

Prior history of:

- Cutaneous reactions to previous anti-cancer therapies
- A dermatological condition
- Allergies
- Dry skin
- Immunosuppression
- Immune-mediated skin conditions
- A high level of sun exposure or radiation treatment
- Advanced age
- Renal and/or hepatic impairment

Patients receiving EV+P should be monitored for skin reactions at each clinic visit, including before each administration[1]

Complete visual inspection and palpation of the skin across the entire body[1,5]

Record and photograph the color, texture, morphology, distribution, and extent of lesions[5]

Monitor the skin for secondary skin infections[1]

Assess for presence of red flag symptoms (e.g., rash or itching that continues to get worse or comes back after treatment, skin blistering or peeling, mucosal involvement: Painful sores or ulcer in mouth or nose, throat, or genital area; fever or flu-like symptoms; and swollen lymph nodes[3]

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AE, adverse event; EV, enfortumab vedotin; P, pembrolizumab; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

1. Pace A et al. *Clin J Oncol Nurs* 2021;25:E1–E9; 2. Dobry AS et al. *JAAD Case Rep* 2021;14:7–9; 3. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 4. Lacouture ME et al. *Oncologist* 2022;27:e223–e232; 5. Barton-Burke M et al. *Nurs Clin North Am* 2017;52:83–113.

Management of skin toxicity

- Routine skin assessments should begin with Cycle 1
- Counsel patients and caregivers to immediately report new or worsening skin reactions

Grade 1

Closely monitor and continue at same dose level with supportive care as clinically indicated (topical emollients, topical corticosteroids, anti-infectives, and topical and oral antihistamines)

Grade 2

- Closely monitor and continue at same dose level with supportive care as clinically indicated (topical emollients, topical corticosteroids, anti-infectives, and topical and oral antihistamines)
- For worsening rash or skin reactions with concomitant fever, hold both agents until grade ≤1 or has returned to baseline, then resume EV treatment at same dose level or reduced by one level, and resume pembrolizumab. Consider specialist referral
- For persistent or recurrent Grade 2, hold both agents until Grade ≤1, then consider reintroduction of EV at same or reduced dose, and resume pembrolizumab. Consider specialist referral

Grade 3

- Hold both agents if rapid onset or worsening symptoms
- Oral or systemic corticosteroids while holding both drugs until complete or partial resolution (Grade ≤1)
  - May supplement with the supportive care recommendations described for Grades 1 and 2 above
- Specialist referral
- Consider skin biopsy to assist with diagnosis
- After improvement to grade ≤1, and either on prednisone ≤10 mg (or equivalent) per day or off corticosteroids
  - Consider reintroduction of EV at same dose level or reduced by one level
  - Consider reintroduction of pembrolizumab depending upon the severity and presentation of the skin reaction

Permanently discontinue both agents for Grade 4 or recurrent Grade 3 skin toxicity

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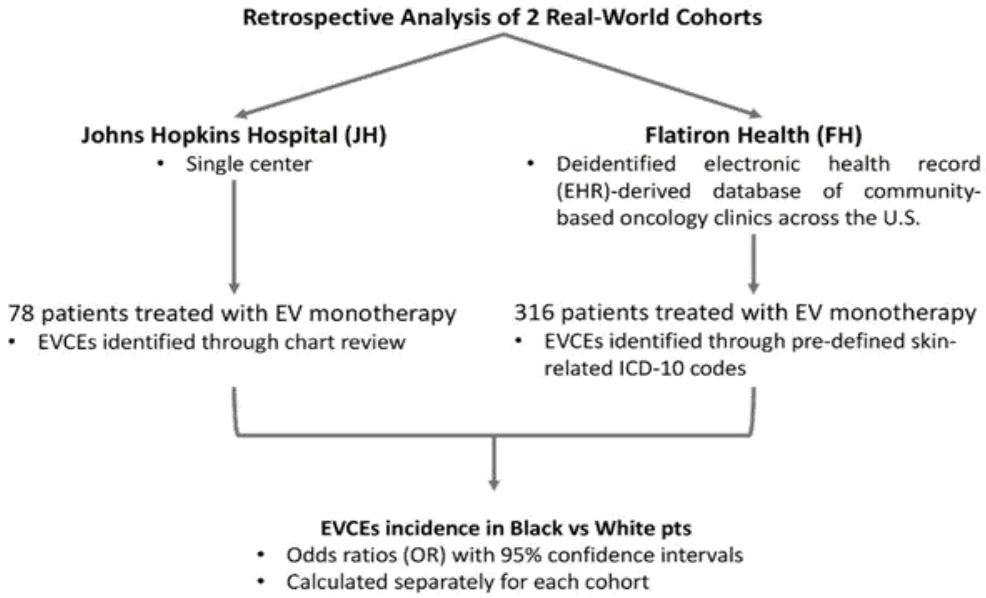
AE, adverse event; EV, enfortumab vedotin; P, pembrolizumab; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Brower B et al. Frontiers in Oncology. 2024;14:1326715.

Incidence of skin toxicity may vary by race

- In this retrospective analysis of real-world patients at Johns Hopkins and the Flatiron Health database, EVCEs were numerically more common among Black patients, though the difference was not statistically significant



n, (%)	No EVCE	EVCE	OR (95% CI)
Johns Hopkins cohort (n=78)			
White	26 (44.8)	32 (55.2)	1.63 (0.44–6.0)
Black	4 (33.3)	8 (66.7)	
Flatiron Health cohort (n=316)			
White	246 (84.2)	46 (15.8)	1.78 (0.67–4.73)
Black	18 (75)	6 (25)	

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CI, confidence interval; EV, enfortumab vedotin, EVCE, EV-related cutaneous adverse events; ICD, International Classification of Diseases; OR, odds ratio; P, pembrolizumab; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Vlachou E, et al. Presented at ASCO GU 2024. Abstract P544.

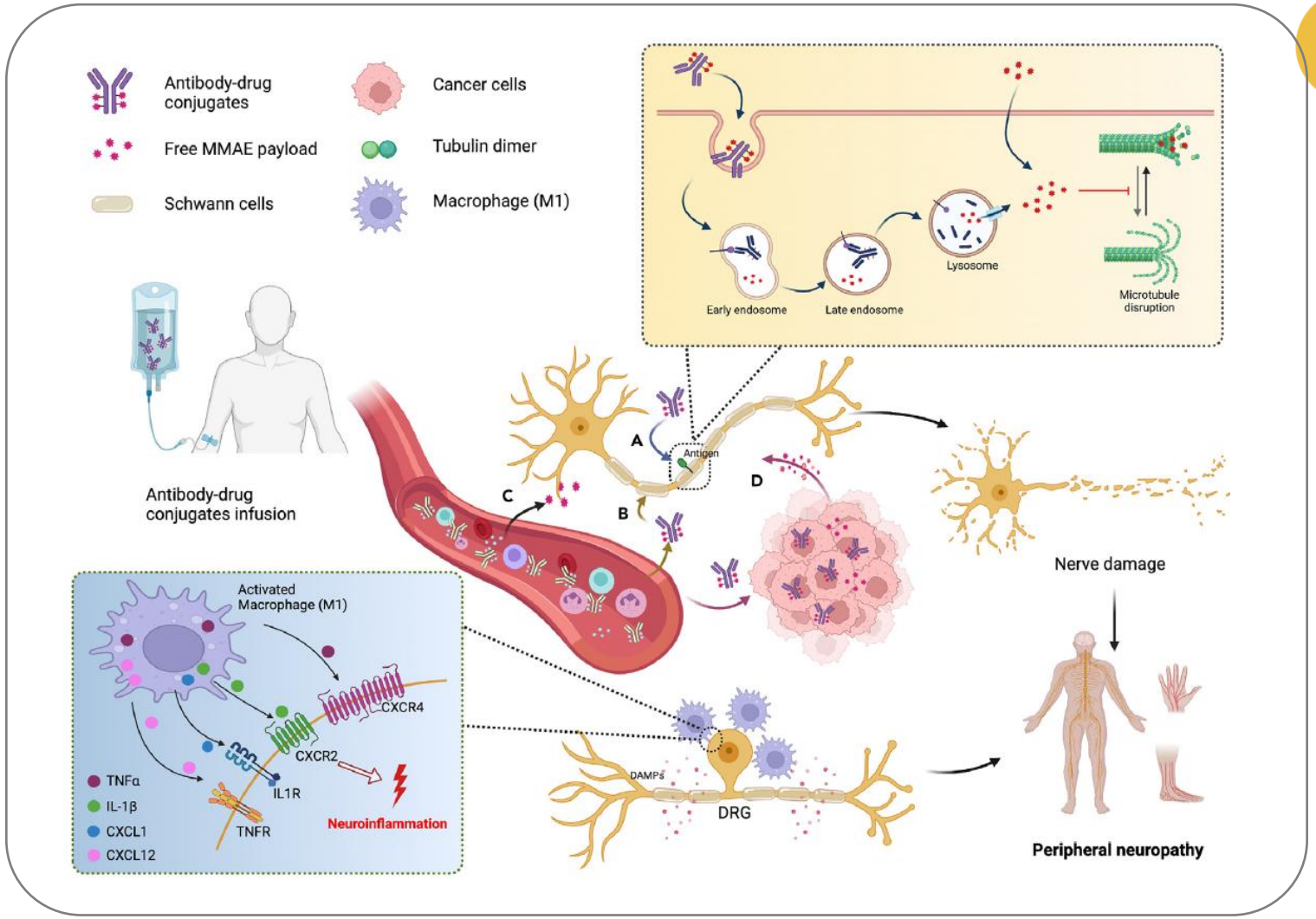
Peripheral neuropathy can occur with MMAE-based ADCs[1,2]

Risk factors[1]

- Comorbidities (e.g., diabetes mellitus)
- Older age
- Spinal involvement of mUC
- Nonmalignant spinal disease

Prevention[1]

- Provide patient education on signs and symptoms
- Monitor closely with early, conservative intervention to prevent peripheral neuropathy from becoming severe



Images reproduced from 'Peripheral neuropathy associated with monomethyl auristatin E-based antibody-drug conjugates' Fu Z et al. iScience. 2023;26(10):107778. Available at: https://www.cell.com/iscience/fulltext/S2589-0042(23)01855-2. By CC: https://creativecommons.org/licenses/by-nc/4.0/

ADC, antibody–drug conjugate; DAMP, damage-associated molecular pattern; DRG, dorsal root ganglion; IL, interleukin; MMAE, monomethyl auristatin; mUC, metastatic urothelial carcinoma; TNF, tumor necrosis factor.

1. Brower B et al. *Front Oncol* 2024;14:1326715; 2. Fu Z et al. *iScience* 2023;26:107778.

PN: Risk factors and monitoring

Median time to onset of Grade ≥2 PN:[1]

6 months

PN is an AESI associated with EV, though it may also occur with P.[1,2] In the EV-302 trial, **63.2% of patients developed EV-related PN, of which 6.8% developed Grade ≥3 PN**[2,3]

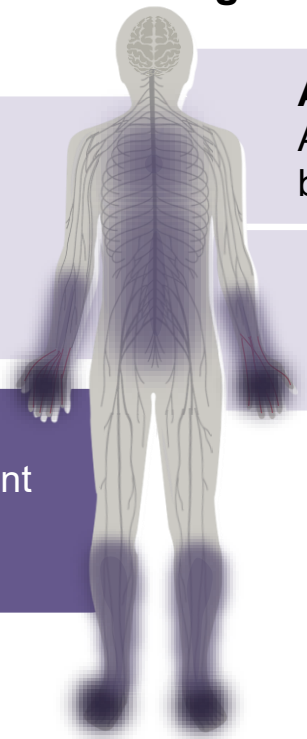
General risk factors[4,5]*

- Pre-existing neuropathy
- Uncontrolled diabetes mellitus
- Pre-existing infection (e.g., HIV)
- Age (≥75 years)
- Family history of neuropathy
- Spinal involvement of mUC
- Non-malignant spinal disease
- Liver/thyroid/kidney disorders
- Autoimmune disease
- Vitamin deficiency
- Smoking
- Alcohol abuse

Screening questions for PN are recommended at each visit for patients receiving EV+P treatment,[1] as PN results from damage caused by anti-cancer therapies[5]

Sensory effects[4]
Typically affect hands and feet

Autonomic effects[4]
Affect involuntary bodily processes



Motor effects[4]
Can progress from sensory effects

Conduct functional assessment of fine motor skills: Observe patient buttoning, zipping, or threading a needle[5]

Conduct functional assessment of gait and balance and assess lower-extremity strength and sensation[5]

Disclaimer: EV+P may not be approved in your region. This content is shared to support proactive AE management of EV (as monotherapy or in combination), not to highlight efficacy.

*In addition to exposure to neurotoxic agents, such as anti-cancer therapies.[1]

AESI, adverse event of special interest; BMI, body mass index; EV, enfortumab vedotin; HIV, human immunodeficiency virus; mUC, metastatic urothelial carcinoma; P, pembrolizumab; PN, peripheral neuropathy.

1. Brower B et al. *Front Oncol* 2024;14:1326715; 2. Powles T et al. *N Engl J Med* 2024;390:875–888 (supplementary appendix); 3. Powles T et al. *N Engl J Med* 2024;390:875–888;
4. Jordan B et al. *Ann Oncol* 2020;31:1306–1319; 5. Pace A et al. *Clin J Oncol Nurs* 2021;25.

Management of peripheral neuropathy

- Evaluate for signs and symptoms of peripheral neuropathy and assess impact on ADLs
- Simple tests (e.g., picking up a coin, buttoning their shirt, or handwriting) can be helpful in assessing the extent of their symptoms
- Patients should be informed about how peripheral neuropathy can manifest and that any numbness and tingling of the hands or feed, muscle weakness (especially in legs, or issues with balance) should be reported immediately

- Urgent neurologist referral if the following are suspected:
- Myasthenia gravis (muscle weakness, dysphagia, ptosis, vision changes)
- Guillain-Barré syndrome (muscle weakness with absent or reduced tendon reflexes)
- Encephalitis (confusion, altered behavior, headaches, seizures)

Grade 1

- Consider proactive dose reduction or dose hold of EV
- Consider holding pembrolizumab (low threshold to hold), monitor symptoms closely for a week
- Consider adjunct treatment with medications for nerve pain (e.g., duloxetine, pregabalin, and gabapentin)

Grade 2

- Withhold EV until Grade ≤1 or return to baseline
  - For first occurrence, resume treatment at the same dose level
  - For recurrent Grade 2, resume treatment reduced by one dose level
- Consider workup for immune-mediated etiology
- Consider adjunct treatment with medications for nerve pain (e.g., duloxetine, pregabalin, and gabapentin)
- Consider physical or occupational therapy

Grade ≥3

- Permanently discontinue both agents
- Specialist referral

Possible immune-related nervous system AE (e.g., symptoms not consistent with peripheral sensory neuropathy)

- Hold pembrolizumab
- Specialist referral and neurological workup

Disclaimer: EV+P may not be approved in your region. This content is shared to support proactive AE management of EV (as monotherapy or in combination), not to highlight efficacy.

ADL, activities of daily living; AE, adverse event; EV, enfortumab vedotin; P, pembrolizumab.

Brower B et al. *Front Oncol* 2024;14:1326715.

Hyperglycemia: Risk factors and monitoring

Median time to onset of hyperglycemia:[1]

0.5 months

Hyperglycemia is an AESI associated with EV+P that occurs infrequently but can become severe or fatal[1]

General risk factors[1]

- Prior diabetes mellitus
- Increased BMI (≥30 kg/m^2)
- Illness/infection
- Use of systemic steroids
- Underlying fatty liver disease

Before initiation of EV (baseline)

Screen for signs of diabetes or hyperglycemia[2]*

Glucose-raising medications

Medications may increase blood glucose levels (including steroids used to treat other AESIs). Close monitoring may be required in these patients[1]

Before each EV dose

Assess blood glucose prior to dosing[2]

Between EV doses

Conduct periodic monitoring of blood glucose throughout course of treatment[2]

Specialist referral

If there is concern for ongoing poor glucose control (e.g., >250 mg/dL) consider referral to an endocrinologist[1]

Disclaimer: EV+P may not be approved in your region.
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*Hyperglycemia occurred more frequently in patients with baseline hyperglycemia or BMI ≥30 kg/m^2. Patients with baseline HbA_{1c} ≥8% were excluded from clinical trials.[2]

AESI, adverse event of special interest; BMI, body mass index; EV, enfortumab vedotin; HbA_{1c}, glycated hemoglobin; P, pembrolizumab.

1. Brower B et al. *Front Oncol* 2024;14:1326715; 2. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

Management of hyperglycemia

- Assess baseline hemoglobin A1C ahead of treatment initiation
- Inform patients about the risk of hyperglycemia with treatment
- Patient education on how to recognize and report associated symptoms
- Ongoing non-fasting glucose monitoring before each dose

If evidence of DKA:
- Hold pembrolizumab until DKA resolves
- Endocrine referral
- Inpatient management
- Manage DKA per guidelines
- Initiate insulin as clinically indicated

Grade 1
- Continue pembrolizumab with close clinical follow-up and laboratory evaluation
- Initiate insulin therapy/anti-hyperglycemic as clinically indicated

Grade 2
- Hold EV until non-fasting blood glucose improved to ≤250 mg/dL; resume EV at same dose level
- Continue pembrolizumab
- Initiate insulin therapy/anti-hyperglycemic as clinically indicated

Grade ≥3
- Hold pembrolizumab and initiate insulin therapy/anti-hyperglycemic as clinically indicated; resume when Grade ≤1
- Hold if non-fasting blood glucose >250 mg/dL
  - Resume EV at same dose level with close monitoring after consultation with medical monitor, when improvement to ≤250 mg/dL, and clinically and metabolically stable
  - If blood glucose >500 mg/dL, interrupt EV to evaluate for underlying diagnosis
- Consider urgent endocrine referral if hyperglycemia is suspected to be related to pembrolizumab
- Inpatient admission for management of any of the following:
  - Concern for developing DKA
  - Symptomatic patients regardless of diabetes type
  - New onset T1DM unable to see endocrinology

Disclaimer: EV+P may not be approved in your region.
This content is shared to support proactive AE management of EV (as monotherapy or in combination), not to highlight efficacy.
Images reproduced from 'Managing potential adverse events during treatment with enfortumab vedotin + pembrolizumab in patients with advanced urothelial cancer' Brower B et al. *Frontiers in Oncology*. 2024;14:1326715. Available at: https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2024.1326715/full. By CC: https://creativecommons.org/licenses/by-nc/4.0/
AE, adverse event; EV, enfortumab vedotin; DKA, diabetic ketoacidosis; P, pembrolizumab; T1DM, type 1 diabetes mellitus.
Brower B et al. *Front Oncol* 2024;14:1326715.

Pneumonitis/ILD: Risk factors and monitoring

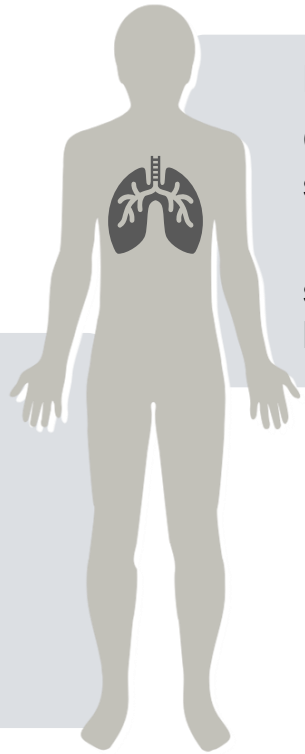
Median time to onset of pneumonitis:[1]

4 months

Pneumonitis/ILD is associated with EV+P, as well as both EV and pembrolizumab as monotherapy; it may be severe, life-threatening, or fatal and occurs at a higher rate during combination therapy[1]

General risk factors[1]

- Prior thoracic radiation (immune-mediated pneumonitis)
- History of underlying pulmonary disease



Prevention[1]

Careful monitoring for any signs or symptoms

Patient education on the symptoms they should immediately raise with their healthcare provider

Symptoms and routine monitoring[1,2]

Monitor patients for signs and symptoms, such as hypoxia, cough, dyspnea, or interstitial infiltrates on radiological examinations

Specialist referral[1]

For severe pneumonitis/ILD, consider referral to pulmonology (if available) for consideration of bronchoscopy and further workup[1]

Disclaimer: EV+P may not be approved in your region. This content is shared to support proactive AE management of EV (as monotherapy or in combination), not to highlight efficacy.

AE, adverse event; EV, enfortumab vedotin; ILD; interstitial lung disease; P, pembrolizumab.

1. Brower B et al. *Front Oncol* 2024;14:1326715; 2. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

Management of pneumonitis

Evaluate patient to exclude other causes of pulmonary signs and symptoms (e.g., infection, disease progression, pulmonary embolism, pleural effusion, sarcoidosis, pulmonary fibrosis, pulmonary edema)

Symptomatic pneumonitis
- Hypoxia
- Cough
- Dyspnea
- Radiological evidence of interstitial infiltrates

Grade 2 →
- Immediately withhold both agents
- Consider referral to pulmonary specialist
- Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent, followed by taper)
- Following corticosteroid taper:
  - Resume pembrolizumab when Grade ≤1
  - Resume EV same dose level or reduced by one level when grade ≤1

Grade ≥3; recurrent Grade 2 →
- Permanently discontinue both agents
- Administer corticosteroids (initial dose of 1–2 mg/kg prednisone or equivalent, followed by taper)
- Urgent referral to pulmonary specialist
- Hospitalize, consider ICU care

EV, enfortumab vedotin; ICU, intensive care unit.
Brower B et al. *Frontiers in Oncology*. 2024;14:1326715.

There is established guidance in the SmPC to help manage AESIs with EV

AESI	SmPC management guidance
Skin reactions	Topical **corticosteroids and antihistamines** can be considered for **mild-to-moderate skin reactions**
	For **suspected SJS or TEN**, or in case of **bullous lesion** onset, **withhold treatment immediately and refer to specialist care**
	For **Grade 2 worsening, Grade 2 with fever, or Grade 3 skin reactions**, treatment should be **withheld until Grade ≤1** and **referral for specialist care** should be considered. • **Resume at the same dose level or consider dose reduction** by one dose level
	Permanently discontinue EV for **confirmed SJS** or **TEN**, or **Grade 4** or **recurrent Grade 3** skin reactions
Hyperglycemia	If **blood glucose is elevated** >13.9 mmol/L (>250 mg/dL), **EV should be withheld** until blood glucose is ≤13.9 mmol/L • **Resume** at the **same dose level**
Peripheral neuropathy	For **Grade 2, withhold until Grade ≤1** • For first occurrence, **resume treatment at the same dose level** • For a recurrence, **withhold until Grade ≤1**, then resume treatment reduced by one dose level
	For **Grade ≥3, permanently discontinue**
Pneumonitis/ILD	For **Grade 2, withhold EV until Grade ≤1** • **Resume** at the **same dose or consider dose reduction**
	Permanently discontinue EV for **Grade ≥3** events or **recurring Grade 2 events**

Dose reduction schedule

Starting dose
1.25 mg/kg
(up to 125 mg)*

First dose reduction
1.00 mg/kg
(up to 100 mg)

Second dose reduction
0.75 mg/kg
(up to 5 mg)

Third dose reduction
0.50 mg/kg
(up to 50 mg)

*Up to a maximum of 125 mg for patients weighing ≥100 kg.
AESI, adverse event of special interest; EV, enfortumab vedotin; ILD; interstitial lung disease; P, pembrolizumab; SJS, Stevens–Johnson syndrome; SmPC, Summary of Product Characteristics; TEN, toxic epidermal necrolysis.
PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

Additional dosing considerations

Liver impairment

- No dose adjustment necessary in patients with mild hepatic impairment
- Hepatic impairment is expected to increase the systemic exposure to MMAE; patients should be closely monitored for potential AEs
- Due to sparsity of data in patients with moderate and severe hepatic impairment, no specific dose recommendation can be given

Renal impairment

- No dose adjustment necessary in patients with mild, moderate, or severe renal impairment.
- Has not been evaluated in patients with end-stage renal disease

BMI

- Recommended dose of EV in combination with pembrolizumab is 1.25 mg/kg
- However, patients with BMI ≥100 kg should not exceed the maximum dose of 125 mg

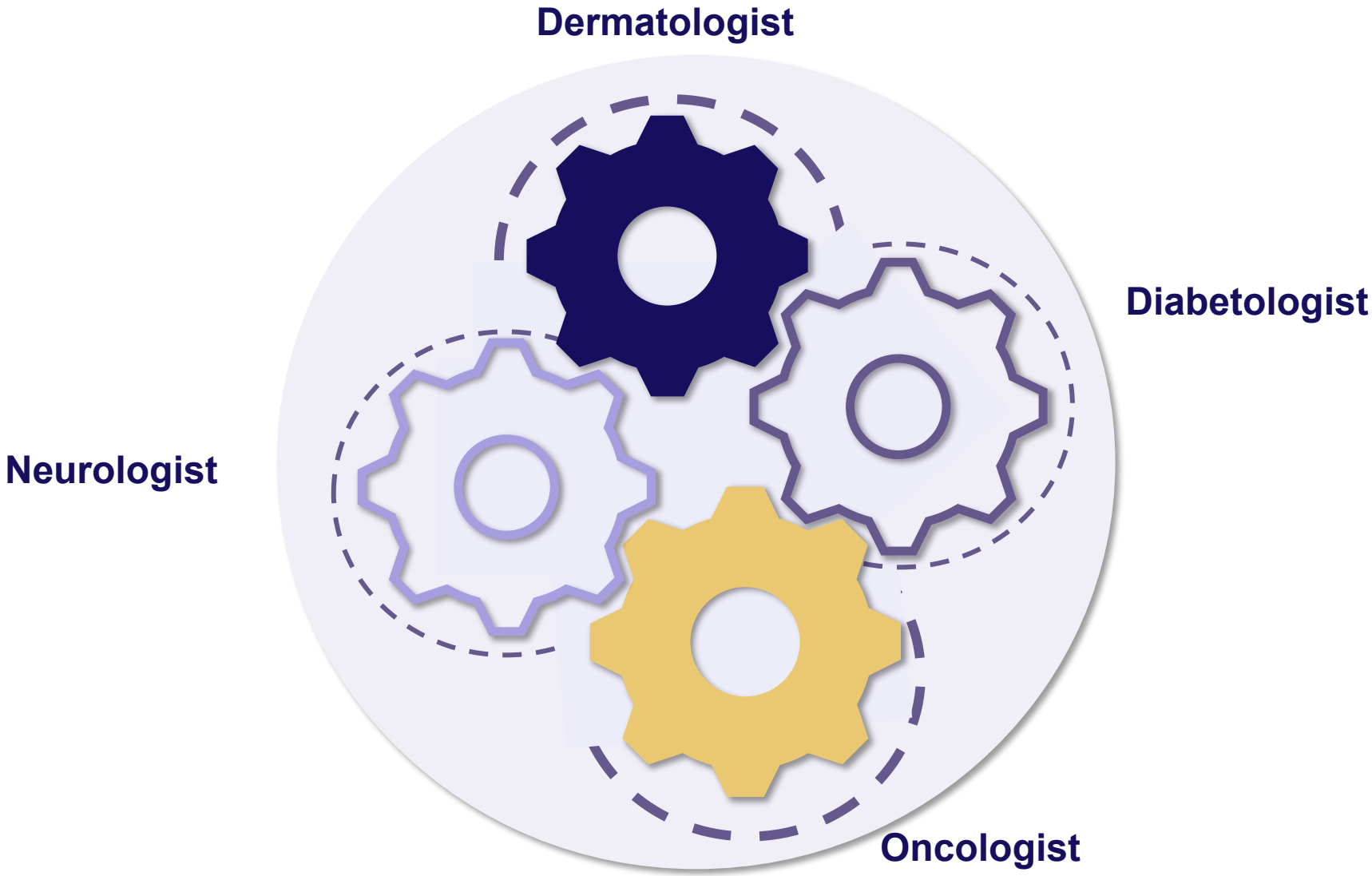
AE, adverse event; BMI, body mass index; EV, enfortumab vedotin; MMAE, monomethyl auristatin E.

PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

A variety of education strategies may be employed to help encourage patients to promptly report AEs:

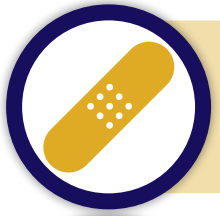
Brower B et al. *Front Oncol* 2024;14:1326715.

Actively involving the MDT and specialists in helping to manage AEs



AE, adverse event; MDT, multidisciplinary team.
Brower B et al. *Front Oncol* 2024;14:1326715.

Summary



Grade ≥3 AEs are less frequent with EV+P vs PBCT, and differ from PBCT's mainly hematologic toxicity profile; AESIs associated with EV include skin reactions, peripheral neuropathy, pneumonitis/ILD, and hyperglycemia[1–3]

Monitoring for AEs during treatment with EV+P is essential to allow for early intervention; this requires effective communication between patients and HCPs, and counselling of patients to emphasize the importance of prompt reporting[4]

Before starting EV+P, the risks and benefits of treatment should be clearly communicated; state that AEs are expected with EV+P, and emphasize the importance of early reporting to aid effective management[4]

Effective communication between specialists should play an active role in the management of AEs to ensure timely identification and effective care[4]

AE, adverse event; AESI, adverse events of special interest; EV, enfortumab vedotin; HCP, healthcare professional; ILD, interstitial lung disease; P, pembrolizumab; PBCT, platinum-based chemotherapy; TRAE, treatment-related adverse event.

1. Powles T et al. *N Engl J Med* 2024;390:875–888; 2. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 3. KEYTRUDA® (pembrolizumab). Summary of Product Characteristics;
4. Brower B et al. *Front Oncol* 2024;14:1326715.

Genitourinary Masterclass

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PI, Prescribing Information

Genitourinary Masterclass

Impact of exposure on response with EV in patients with LA/mUC

Professor Daniel Petrylak
Director of Genitourinary Oncology, Yale University Cancer Center, New Haven, USA

EV as first-line therapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer. Combination therapy with pembrolizumab.

EV as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 or programmed death-ligand 1 inhibitor, and have received a platinum-containing chemotherapy

1L, first line; EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma; P, pembrolizumab;
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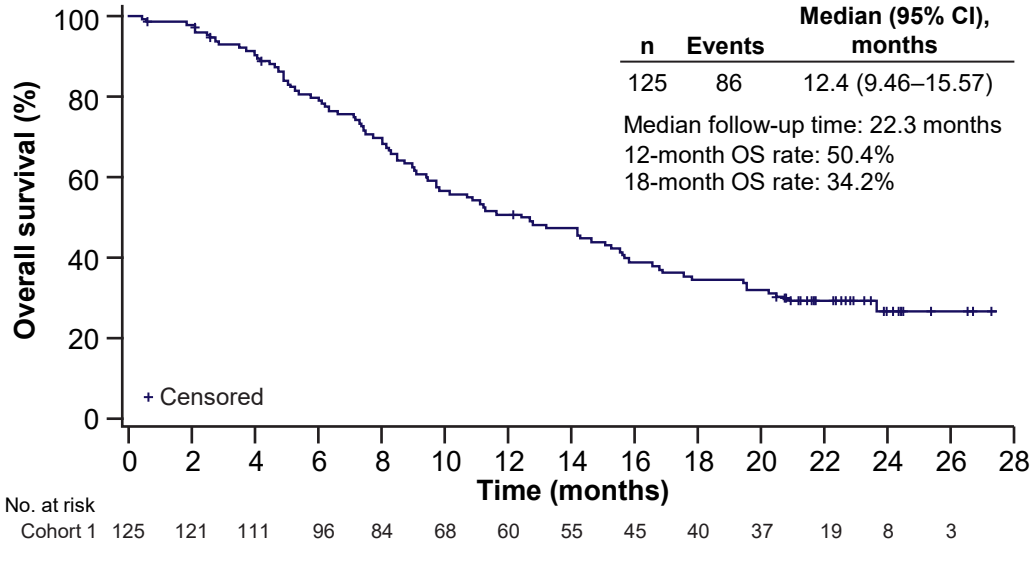
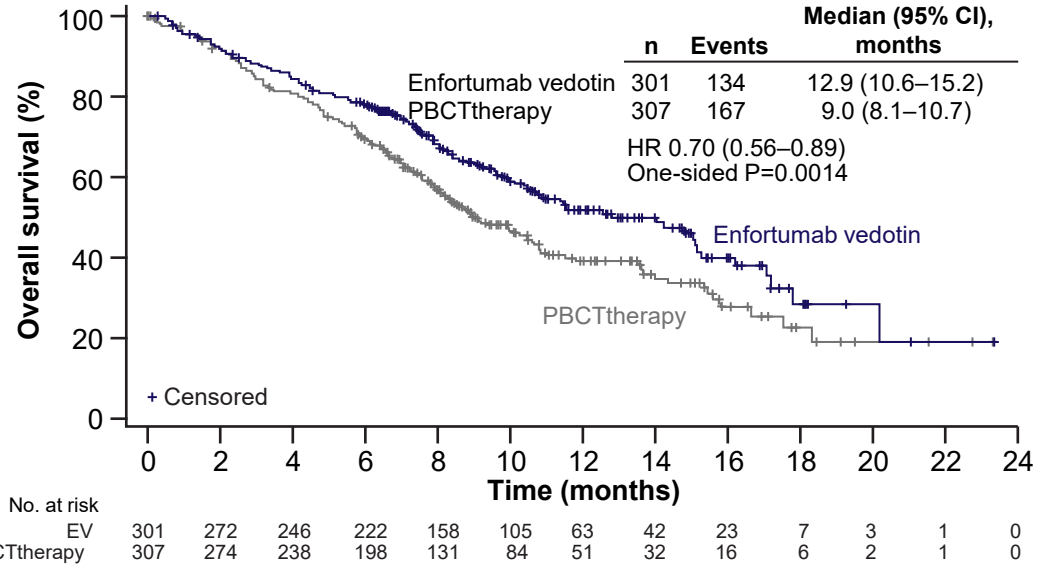
EV monotherapy 1.25 mg/kg 3Q4W has shown consistent clinical activity to patients with LA/mUC in the 2L+ setting

Overall survival (EV-201 cohort 1)



Overall survival (EV-301)



	EV-201 Cohort 1 (n=125)	EV-201 Cohort 2 (n=89)	EV-301 EV arm (n=301)
ORR, % (95% CI)	44 (35.1–53.2)	52 (41–62)	41 (35–47)
Time to response (range/IQR), months	1.8 (range: 1.2–9.2)	1.8 (IQR: 1.7–1.9)	1.9 (range: 1.1–5.7)
Median DOR (95% CI), months	7.6 (6.3–NR)	10.9 (5.8–NR)	7.4 (5.6–9.5)
Median PFS (95% CI), months	5.8 (4.9–7.5)	5.8 (5.0–8.3)	5.6 (5.3–5.8)
Median OS (95% CI), months	12.4 (9.5–15.6)	14.7 (10.5–18.2)	12.9 (11–15.2)

Data for illustrative purposes only; trials not to be compared directly

3Q4W, Days 1, 8, and 15 of a 28-day cycle; CI, confidence interval; DOR, duration of response; EV, enfortumab vedotin; HR, hazard ratio; IQR, interquartile range; LA/mUC, locally advanced/metastatic urothelial carcinoma; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

EV monotherapy 1.25 mg/kg 3Q4W has an established safety profile from multiple trials of patients with LA/mUC

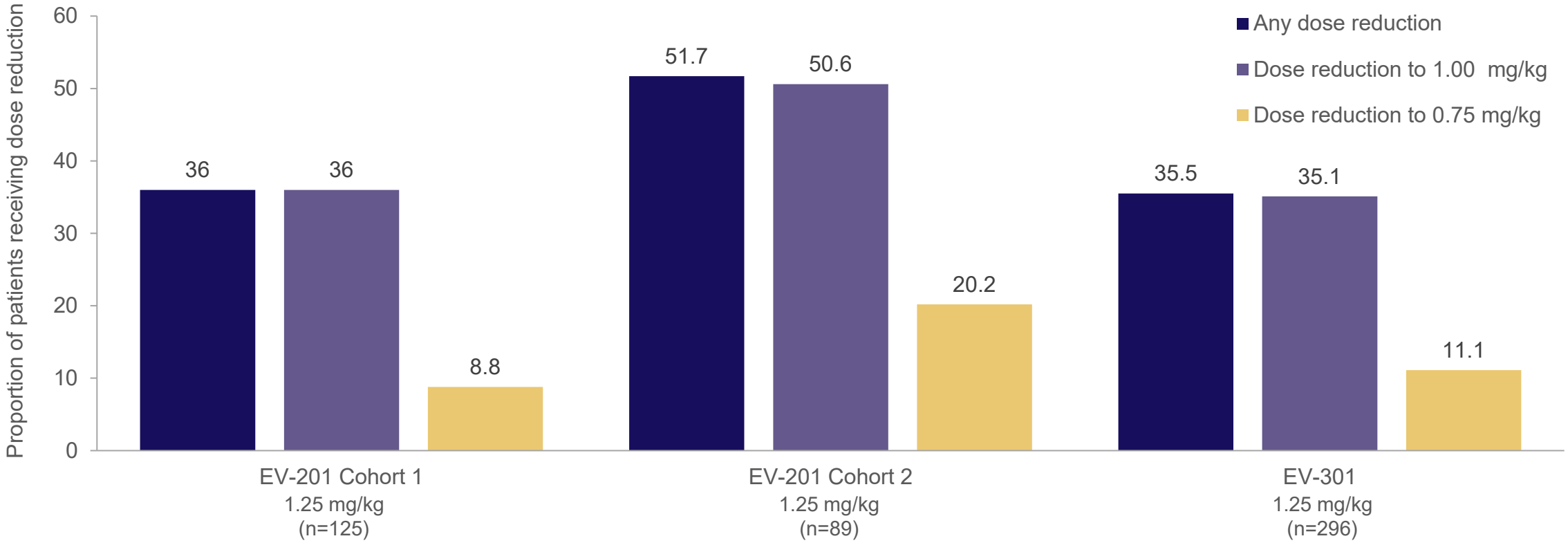
TRAE, n (%)	EV-201 cohort 1 (n=125)	EV-201 cohort 2 (n=89)	EV-301, EV arm (n=296)
Any TRAE	117 (94)	86 (97)	278 (94)
TRAE resulting in dose reduction	40 (32)	41 (46)	96 (32)
TRAE resulting in discontinuation	15 (12)	14 (16)	40 (14)
TRAEs with incidence ≥25% in any study			
Alopecia	61 (49)	45 (51)	135 (46)
Peripheral sensory neuropathy	50 (40)	42 (47)	103 (35)
Pruritus	33 (26)*	27 (30)	96 (32)
Fatigue	62 (50)	30 (34)	93 (31)
Decreased appetite	55 (44)	29 (33)	92 (31)
Diarrhoea	40 (32)	20 (22)	74 (25)
Dysgeusia	50 (40)	24 (27)	73 (25)
Nausea	49 (39)	20 (22)	71 (24)
Maculopapular rash	27 (22)	27 (30)	50 (17)
Anaemia	22 (18)	22 (25)	34 (11)

Data for illustrative purposes only; trials not to be compared directly

*Includes 'pruritus generalised', so patients may be counted more than once.
3Q4W, Days 1, 8, and 15 of a 28-day cycle; EV, enfortumab vedotin; LA/mUC, locally advanced or metastatic urothelial cancer; TRAE, treatment-related adverse event.
Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

Protocol-recommended dose reductions were used to manage AEs in pivotal trials

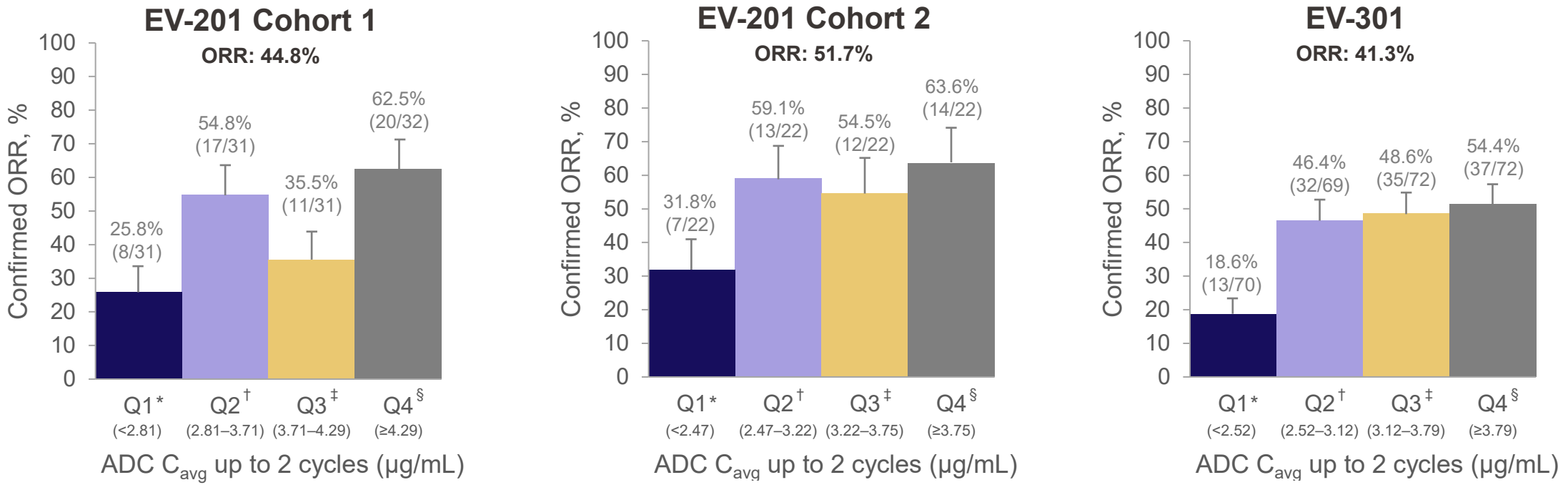
- EV monotherapy was administered at 1.25 mg/kg 3Q4W IV in the pivotal trials and modified per investigator judgement using prespecified guidelines to manage treatment-emergent AEs



Slide adapted from Petrylak D et al. 2024.
All data presented are from a *post hoc* exploratory analysis.
3Q4W, one dose every week for 3 weeks, followed by 1 week without dosing; AE, adverse event; EV, enfortumab vedotin; IV, intravenous.
Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

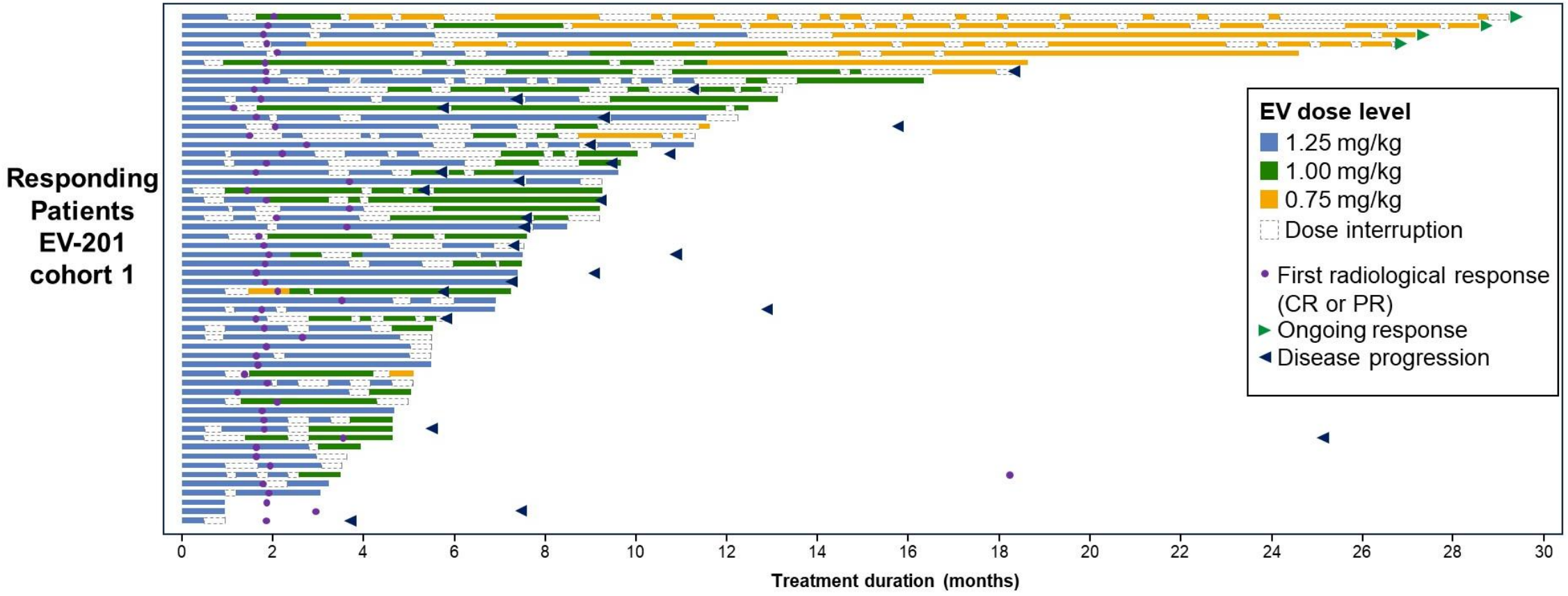
Patients initiating EV monotherapy at 1.25 mg/kg have a higher response than patients initiating at lower doses

- Initial EV doses at 1.25 mg/kg 3Q4W were generally associated with a greater probability of response vs. lower doses in EV-201 Cohort 1, EV-201 Cohort 2, and EV-301
- Patients can continue to respond to EV even with later dose reductions resulting from AEs



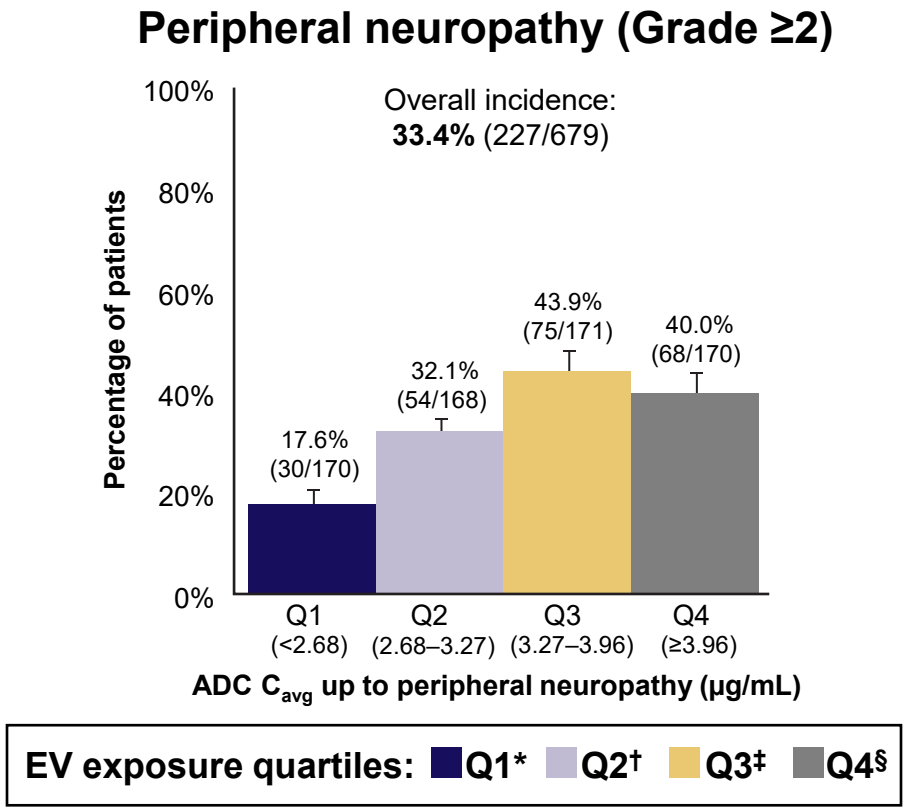
All data presented are from a *post hoc* exploratory analysis. Average ADC exposures were divided into 4 quartiles.
*Q1 represents the EV exposures between 0–25%; †Q2: 25–50%; ‡Q3: 50–75%; §Q4: 75–100% (the highest EV exposure quartile).
ADC, antibody–drug conjugate; AE, adverse event; C_{avg}, time-averaged exposure up to 2 cycles; EV, enfortumab vedotin; ORR, overall response rate.
Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

Patients responding to EV continue to benefit following dose interruptions and reductions



Slide adapted from Petrylak D et al. Presented at ASCO 2024. Abstract 4503.
All data presented are from a post hoc, exploratory analysis.
CR, complete response; EV, enfortumab vedotin; PR, partial response.
Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

Safety correlated with EV monotherapy exposure, indicating that dose modifications are an effective way to manage AEs



- Lower EV exposure was associated with a significantly lower risk ($p<0.0001$) of:
  - Skin reactions¶ (Grade ≥3: 12.5%); median time to onset: 0.6 months
  - Hyperglycaemia (Grade ≥3: 7.1%); median time to onset: 0.6 months
  - Peripheral neuropathy (Grade ≥2: 33.4%); median time to onset: 4.7 months
- Earlier time to onset of skin reactions and hyperglycaemia (median time to onset occurred during Cycle 1) confounded the interpretation of exposure–safety results
- Unconjugated MMAE C_{avg} was not strongly correlated with the incidence of these AEs

Slide adapted from Petrylak D et al. Presented at ASCO 2024. Abstract 4503.
All data presented are from a *post hoc*, exploratory analysis.
Average EV exposures were divided into four quartiles: *Q1 represents EV exposures between 0–25%; †Q2: 25–50%; ‡Q3: 50–75%; §Q4: 75–100% (the highest EV exposure quartile); ¶Composite term.
ADC, antibody–drug conjugate; AE, adverse event; C_{avg}, time-averaged exposure; EV, enfortumab vedotin; MMAE, monomethyl auristatin E; Q, quartile.
Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

In EV-301, durable responses were maintained regardless of dose modifications

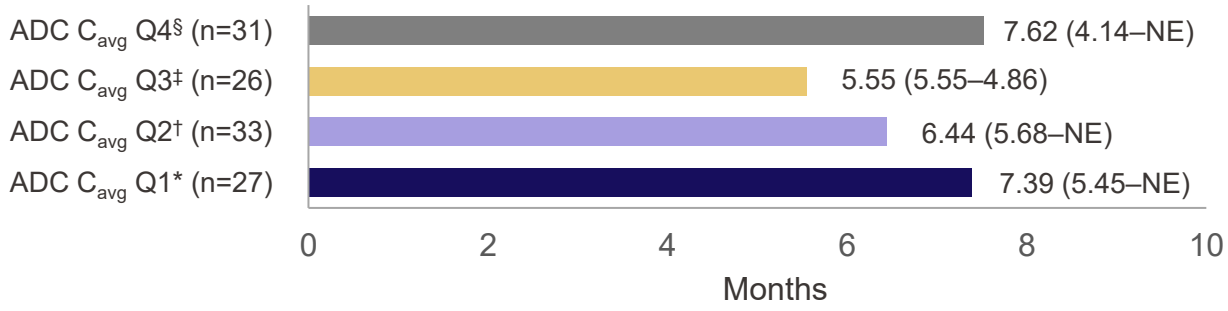
- EV dose reductions/interruptions may allow patients to receive the benefits of EV for as long as possible, and continue to maximise clinical benefits with EV
- EV monotherapy continued to show benefit vs chemotherapy across exposure quartiles

	ADC C_{avg} Q1* (n=74)	ADC C_{avg} Q2† (n=74)	ADC C_{avg} Q3‡ (n=74)	ADC C_{avg} Q4§ (n=74)
Median EV ADI (mg/kg/4 week)¶ (range)	2.37 (1.15–3.77)	2.96 (1.57–3.82)	3.26 (2.36–3.86)	3.59 (2.50–3.93)
Any EV dose delay (%)	59.5	58.1	44.6	26.4
Any EV dose reduction (%)	54.1	39.2	28.4	20.3
To 1.0 mg/kg	52.7	39.2	28.4	20.3
To 0.75 mg/kg	21.6	14.9	6.8	1.4
Median time to EV dose reduction (range), months	2.02 (0.79–9.27)	2.96 (0.95–12)	3.06 (0.72–6.64)	2.79 (0.89–9.04)

EV-301:

- ORR: 41%
- Median time to response: 1.9 months (range: 1.1–5.7)

Median DOR for responders by exposure quartile (95% CI)



Slide adapted from Petrylak D et al. Presented at ASCO 2024. Abstract 4503.
All data presented are from a *post hoc*, exploratory analysis.
ADC, antibody–drug conjugate; AE, adverse event; C_{avg}, time-averaged exposure; EV, enfortumab vedotin; ORR, overall response rate.
Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

Summary

- EV monotherapy at the 1.25 mg/kg 3Q4W dose shows a manageable safety profile across multiple trials
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3Q4W, one dose every week for 3 weeks, followed by 1 week without dosing; AE, adverse event; EV, enfotumab vedotin; OS, overall survival; PFS, progression-free survival.
Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

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PI, Prescribing Information

Genitourinary Masterclass

Impact of exposure on response with EV in patients with LA/mUC

Professor Daniel Petrylak
Director of Genitourinary Oncology, Yale University Cancer Center, New Haven, USA

EV as first-line therapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer. Combination therapy with pembrolizumab.

EV as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 or programmed death-ligand 1 inhibitor, and have received a platinum-containing chemotherapy

1L, first line; EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma; P, pembrolizumab;
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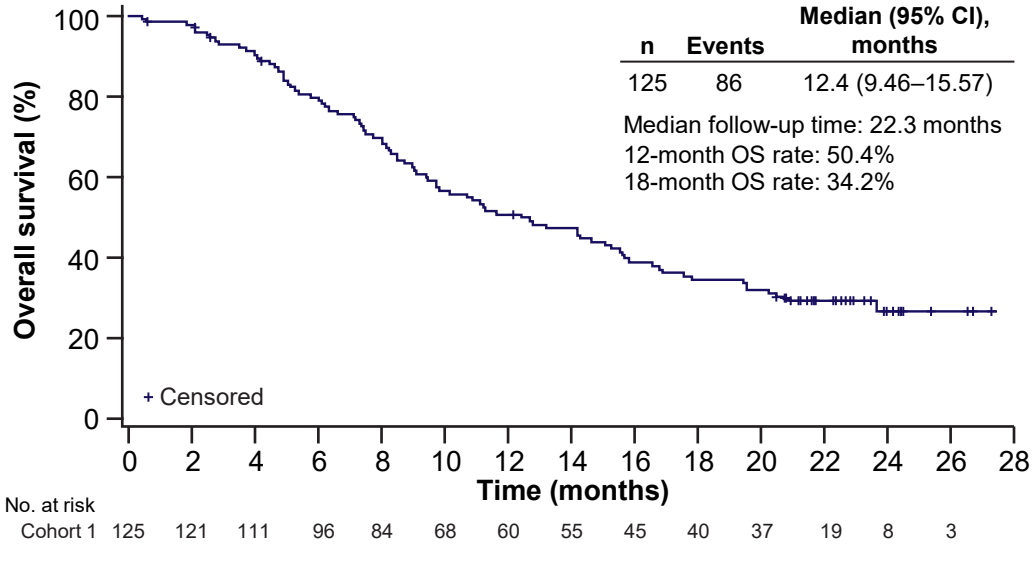
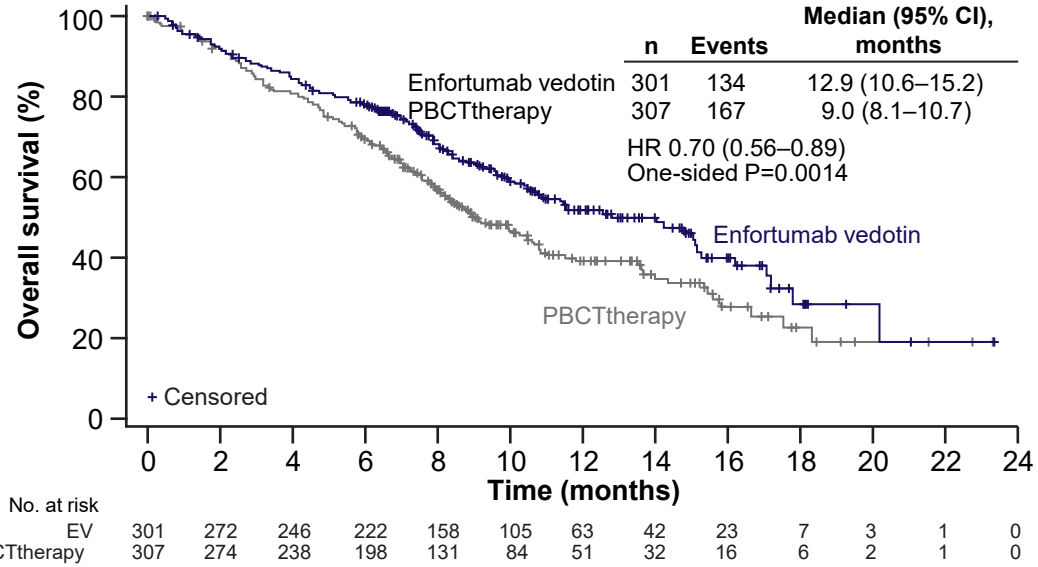
EV monotherapy 1.25 mg/kg 3Q4W has shown consistent clinical activity to patients with LA/mUC in the 2L+ setting

Overall survival (EV-201 cohort 1)



Overall survival (EV-301)



	EV-201 Cohort 1 (n=125)	EV-201 Cohort 2 (n=89)	EV-301 EV arm (n=301)
ORR, % (95% CI)	44 (35.1–53.2)	52 (41–62)	41 (35–47)
Time to response (range/IQR), months	1.8 (range: 1.2–9.2)	1.8 (IQR: 1.7–1.9)	1.9 (range: 1.1–5.7)
Median DOR (95% CI), months	7.6 (6.3–NR)	10.9 (5.8–NR)	7.4 (5.6–9.5)
Median PFS (95% CI), months	5.8 (4.9–7.5)	5.8 (5.0–8.3)	5.6 (5.3–5.8)
Median OS (95% CI), months	12.4 (9.5–15.6)	14.7 (10.5–18.2)	12.9 (11–15.2)

Data for illustrative purposes only; trials not to be compared directly

3Q4W, Days 1, 8, and 15 of a 28-day cycle; CI, confidence interval; DOR, duration of response; EV, enfortumab vedotin; HR, hazard ratio; IQR, interquartile range; LA/mUC, locally advanced/metastatic urothelial carcinoma; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

EV monotherapy 1.25 mg/kg 3Q4W has an established safety profile from multiple trials of patients with LA/mUC

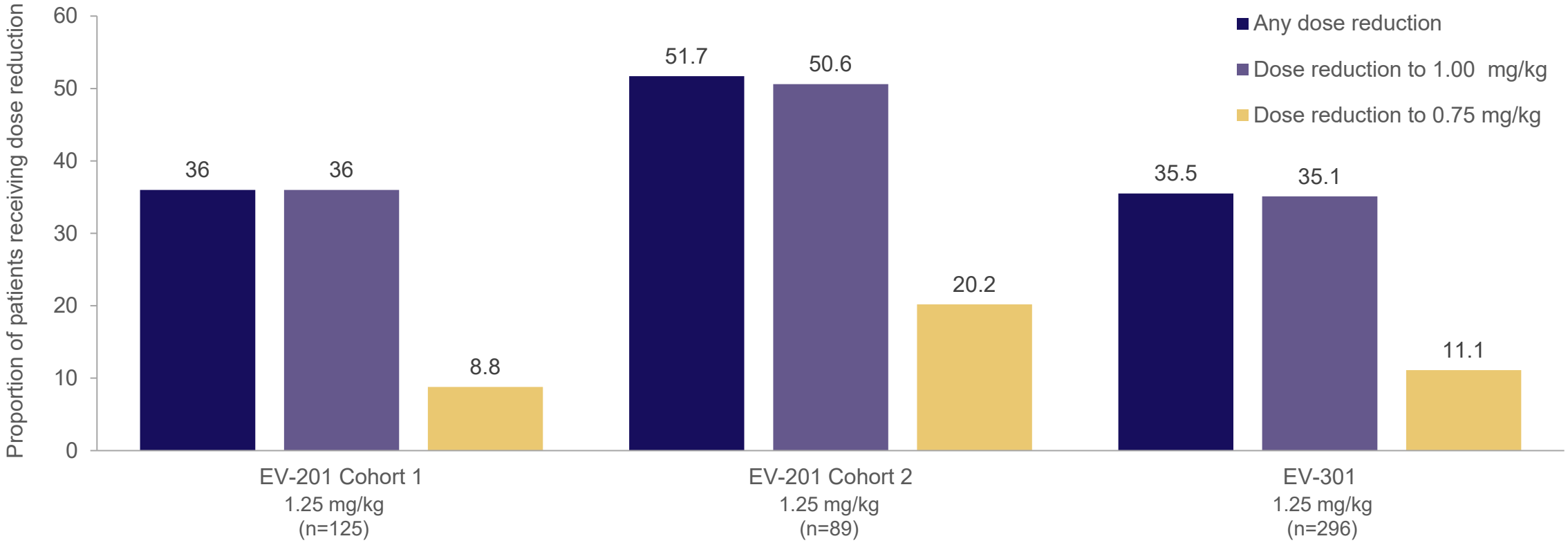
TRAE, n (%)	EV-201 cohort 1 (n=125)	EV-201 cohort 2 (n=89)	EV-301, EV arm (n=296)
Any TRAE	117 (94)	86 (97)	278 (94)
TRAE resulting in dose reduction	40 (32)	41 (46)	96 (32)
TRAE resulting in discontinuation	15 (12)	14 (16)	40 (14)
TRAEs with incidence ≥25% in any study			
Alopecia	61 (49)	45 (51)	135 (46)
Peripheral sensory neuropathy	50 (40)	42 (47)	103 (35)
Pruritus	33 (26)*	27 (30)	96 (32)
Fatigue	62 (50)	30 (34)	93 (31)
Decreased appetite	55 (44)	29 (33)	92 (31)
Diarrhoea	40 (32)	20 (22)	74 (25)
Dysgeusia	50 (40)	24 (27)	73 (25)
Nausea	49 (39)	20 (22)	71 (24)
Maculopapular rash	27 (22)	27 (30)	50 (17)
Anaemia	22 (18)	22 (25)	34 (11)

Data for illustrative purposes only; trials not to be compared directly

*Includes 'pruritus generalised', so patients may be counted more than once.
3Q4W, Days 1, 8, and 15 of a 28-day cycle; EV, enfortumab vedotin; LA/mUC, locally advanced or metastatic urothelial cancer; TRAE, treatment-related adverse event.
Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

Protocol-recommended dose reductions were used to manage AEs in pivotal trials

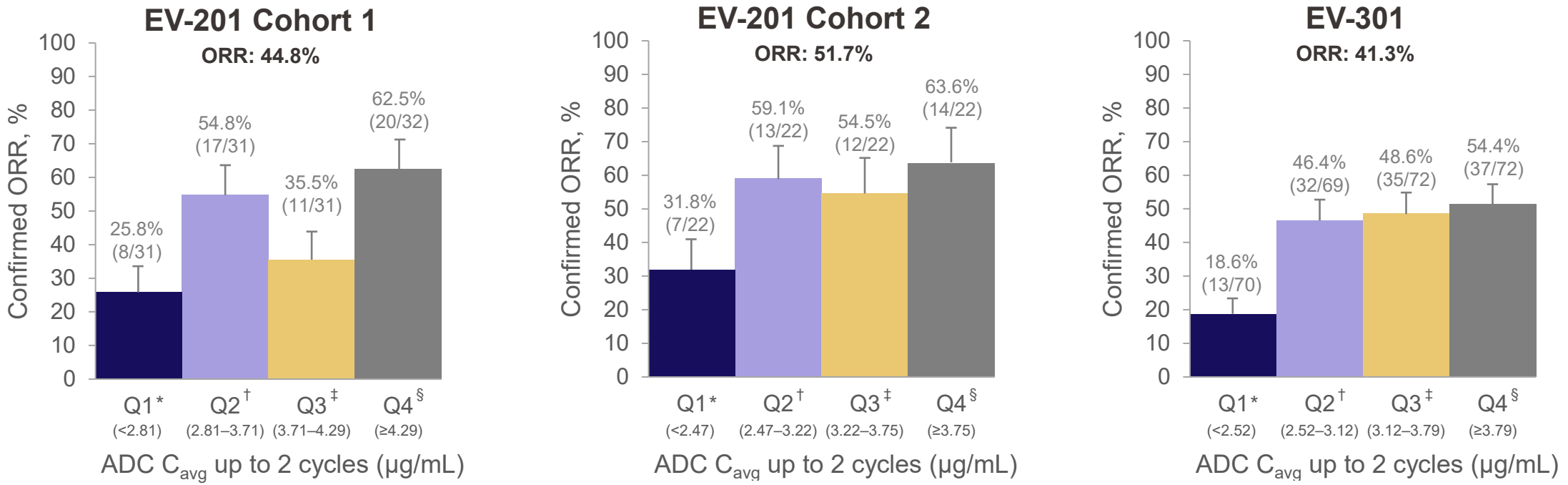
- EV monotherapy was administered at 1.25 mg/kg 3Q4W IV in the pivotal trials and modified per investigator judgement using prespecified guidelines to manage treatment-emergent AEs



Slide adapted from Petrylak D et al. 2024.
All data presented are from a *post hoc* exploratory analysis.
3Q4W, one dose every week for 3 weeks, followed by 1 week without dosing; AE, adverse event; EV, enfortumab vedotin; IV, intravenous.
Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

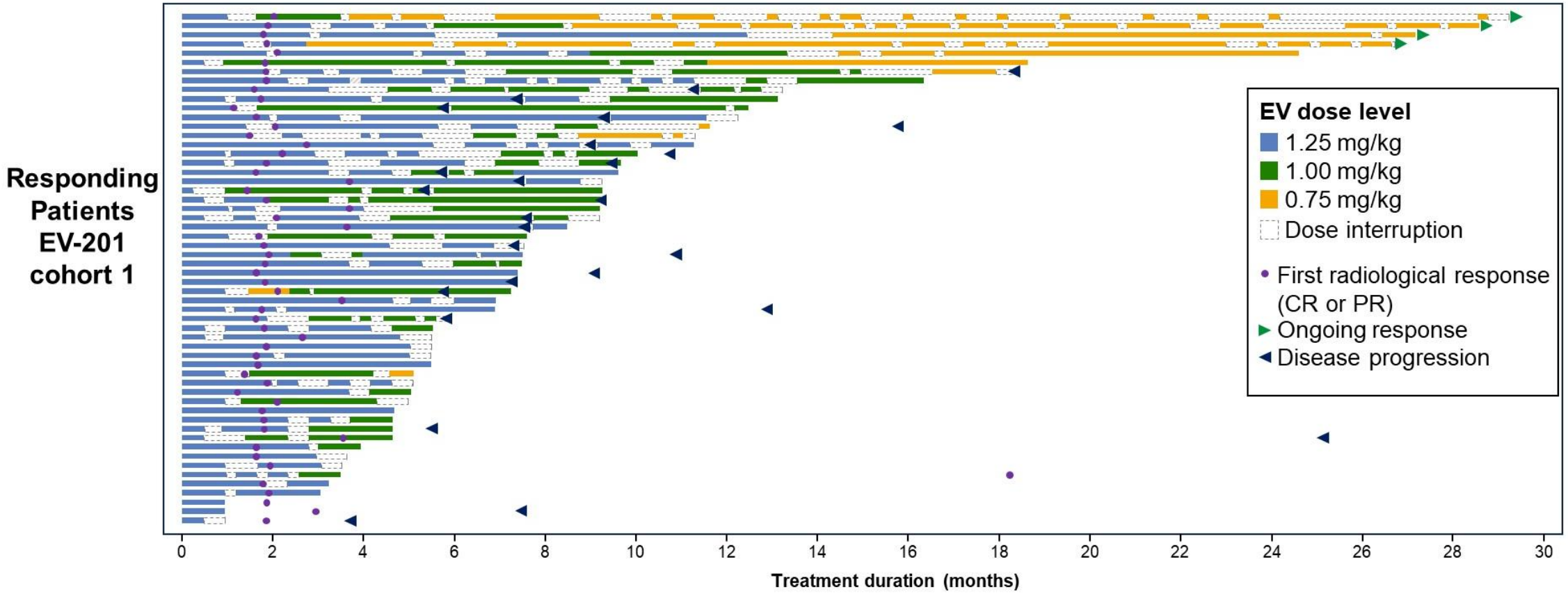
Patients initiating EV monotherapy at 1.25 mg/kg have a higher response than patients initiating at lower doses

- Initial EV doses at 1.25 mg/kg 3Q4W were generally associated with a greater probability of response vs. lower doses in EV-201 Cohort 1, EV-201 Cohort 2, and EV-301
- Patients can continue to respond to EV even with later dose reductions resulting from AEs



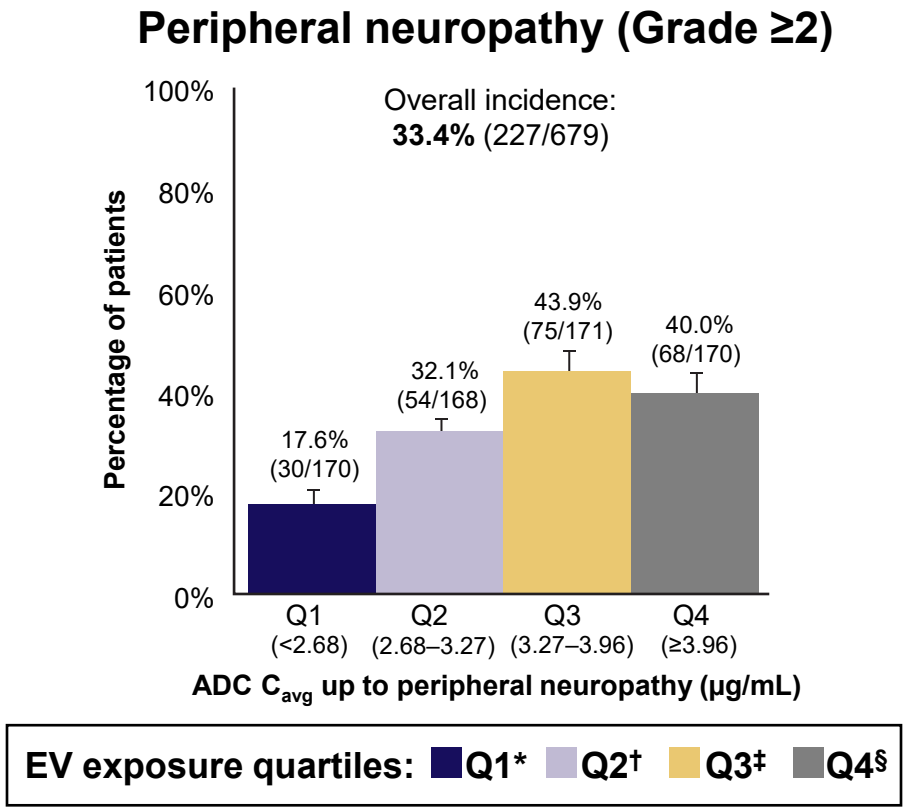
All data presented are from a *post hoc* exploratory analysis. Average ADC exposures were divided into 4 quartiles.
*Q1 represents the EV exposures between 0–25%; †Q2: 25–50%; ‡Q3: 50–75%; §Q4: 75–100% (the highest EV exposure quartile).
ADC, antibody–drug conjugate; AE, adverse event; C_{avg}, time-averaged exposure up to 2 cycles; EV, enfortumab vedotin; ORR, overall response rate.
Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

Patients responding to EV continue to benefit following dose interruptions and reductions



Slide adapted from Petrylak D et al. Presented at ASCO 2024. Abstract 4503.
All data presented are from a post hoc, exploratory analysis.
CR, complete response; EV, enfortumab vedotin; PR, partial response.
Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

Safety correlated with EV monotherapy exposure, indicating that dose modifications are an effective way to manage AEs



- Lower EV exposure was associated with a significantly lower risk ($p<0.0001$) of:
  - Skin reactions¶ (Grade ≥3: 12.5%); median time to onset: 0.6 months
  - Hyperglycaemia (Grade ≥3: 7.1%); median time to onset: 0.6 months
  - Peripheral neuropathy (Grade ≥2: 33.4%); median time to onset: 4.7 months
- Earlier time to onset of skin reactions and hyperglycaemia (median time to onset occurred during Cycle 1) confounded the interpretation of exposure–safety results
- Unconjugated MMAE C_{avg} was not strongly correlated with the incidence of these AEs

Slide adapted from Petrylak D et al. Presented at ASCO 2024. Abstract 4503.
All data presented are from a *post hoc*, exploratory analysis.
Average EV exposures were divided into four quartiles: *Q1 represents EV exposures between 0–25%; †Q2: 25–50%; ‡Q3: 50–75%; §Q4: 75–100% (the highest EV exposure quartile); ¶Composite term.
ADC, antibody–drug conjugate; AE, adverse event; C_{avg}, time-averaged exposure; EV, enfortumab vedotin; MMAE, monomethyl auristatin E; Q, quartile.
Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

In EV-301, durable responses were maintained regardless of dose modifications

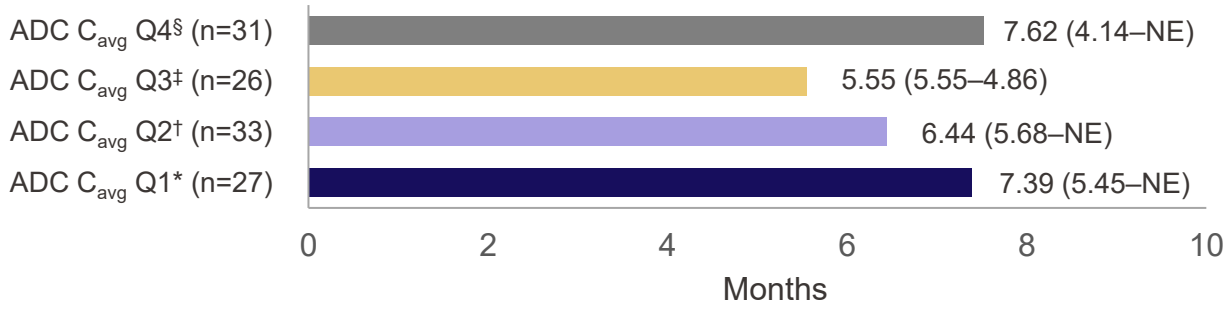
- EV dose reductions/interruptions may allow patients to receive the benefits of EV for as long as possible, and continue to maximise clinical benefits with EV
- EV monotherapy continued to show benefit vs chemotherapy across exposure quartiles

	ADC C_{avg} Q1* (n=74)	ADC C_{avg} Q2† (n=74)	ADC C_{avg} Q3‡ (n=74)	ADC C_{avg} Q4§ (n=74)
Median EV ADI (mg/kg/4 week)¶ (range)	2.37 (1.15–3.77)	2.96 (1.57–3.82)	3.26 (2.36–3.86)	3.59 (2.50–3.93)
Any EV dose delay (%)	59.5	58.1	44.6	26.4
Any EV dose reduction (%)	54.1	39.2	28.4	20.3
To 1.0 mg/kg	52.7	39.2	28.4	20.3
To 0.75 mg/kg	21.6	14.9	6.8	1.4
Median time to EV dose reduction (range), months	2.02 (0.79–9.27)	2.96 (0.95–12)	3.06 (0.72–6.64)	2.79 (0.89–9.04)

EV-301:

- ORR: 41%
- Median time to response: 1.9 months (range: 1.1–5.7)

Median DOR for responders by exposure quartile (95% CI)



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Practical Guidance on management of cutaneous toxicities from enfortumab vedotin

Dr Kirsten Yeo
Head and Senior Consultant, Dermatology, Singapore General Hospital, Singapore

Dr Johan Chan
Consultant, Division of Medical Oncology, National Cancer Centre Singapore, Singapore

EV as first-line therapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer. Combination therapy with pembrolizumab.

EV as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 or programmed death-ligand 1 inhibitor, and have received a platinum-containing chemotherapy

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Speaker disclosures

Dr Kirsten Yeo

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Dr Johan Chan

Speaker Bureau/Honoraria:

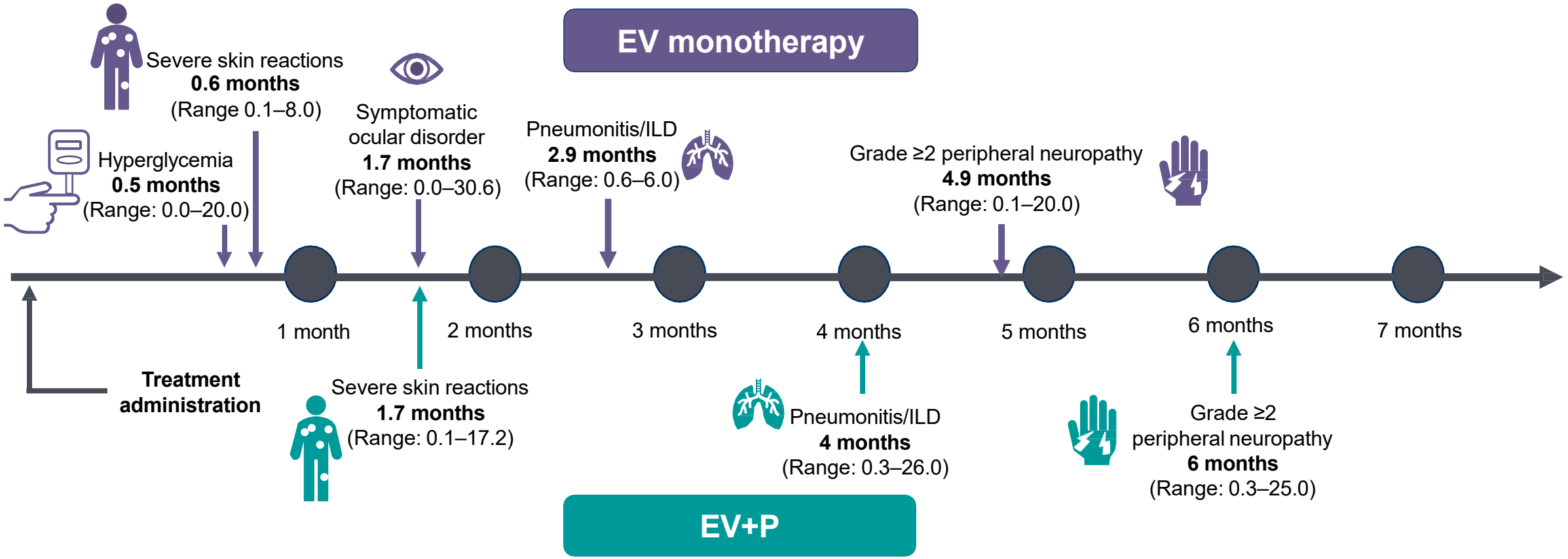
- Astellas, AZ, Bayer, Janssen, Novartis, Pfizer

Scientific Advisory board:

- Bayer, Merck, Pfizer

Onset of Select AEs: EV monotherapy vs EV+P showed delayed onset of select AEs for EV+P combined therapy

Median time to onset of select AEs for EV monotherapy* and EV+P†



*Data reflect the safety population, which includes patients with urothelial carcinoma who received at least one dose of EV 1.25 mg/kg as a single-agent from the EV-101, EV-102, EV-103, EV-201, and EV-301 trials (N=720). Ocular disorders reflect 384 patients with urothelial carcinoma from EV-201, EV-101, and EV-102. †Data reflect pooled safety populations of patients with urothelial cancer who received at least one dose of EV in combination with pembrolizumab at 1.25 mg/kg in EV-302 and EV-103.

AE, adverse event; EV, enfortumab vedotin; EV+P, enfortumab vedotin + pembrolizumab; ILD, interstitial lung disease.

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Cutaneous toxicities of EV

EV, enfortumab vedotin.

Introduction

Skin toxicities are common with EV[1,2]

Skin reactions in a pooled analysis of 793 patients with LA/mUC treated with EV 1.25 mg/kg in clinical studies[1]

Incidence

57% had skin reactions

14% had severe (Grade 3–4) skin reactions

Median time to onset (severe skin reactions)

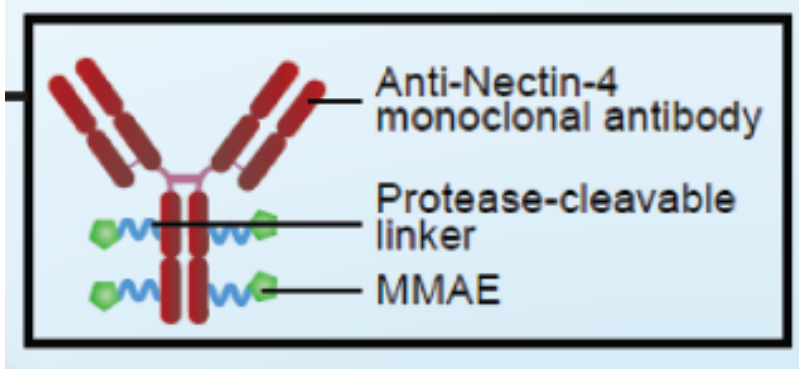
0.7 months (range: 0.1–8.2 months)

Skin reactions may cause significant morbidity, treatment interruption/cessation/dose reduction[1,2]

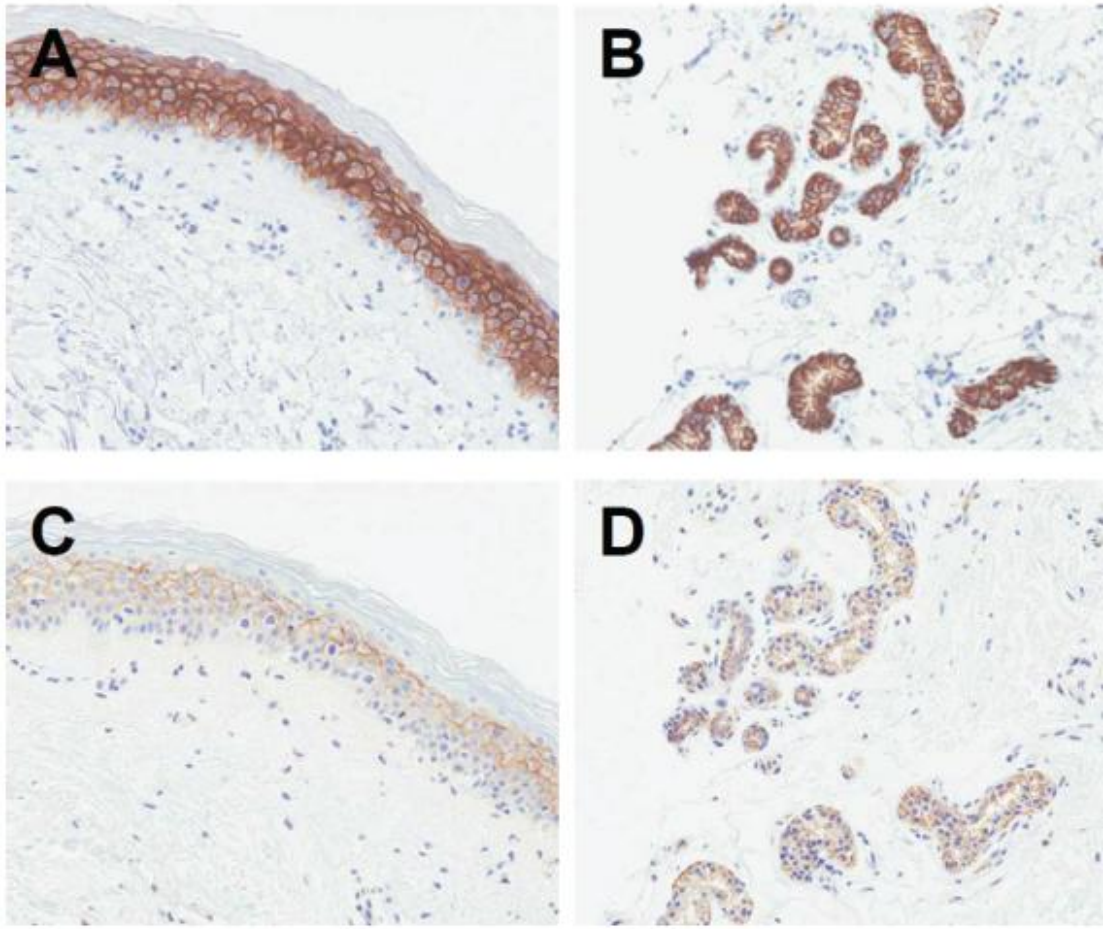
EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma.

1. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 2. Lacouture ME, et al. *Oncologist* 2022;27:e223-e232.

Mechanism of cutaneous toxicity: Off-target effects



- Nectin is expressed in the epidermis and appendages e.g., sweat glands, hair follicles
- Mediates cell-cell adhesion and regular cellular activities including differentiation, proliferation and survival
- Actively dividing epidermal keratinocytes are particularly susceptible to anti-mitotic effects of MMAE



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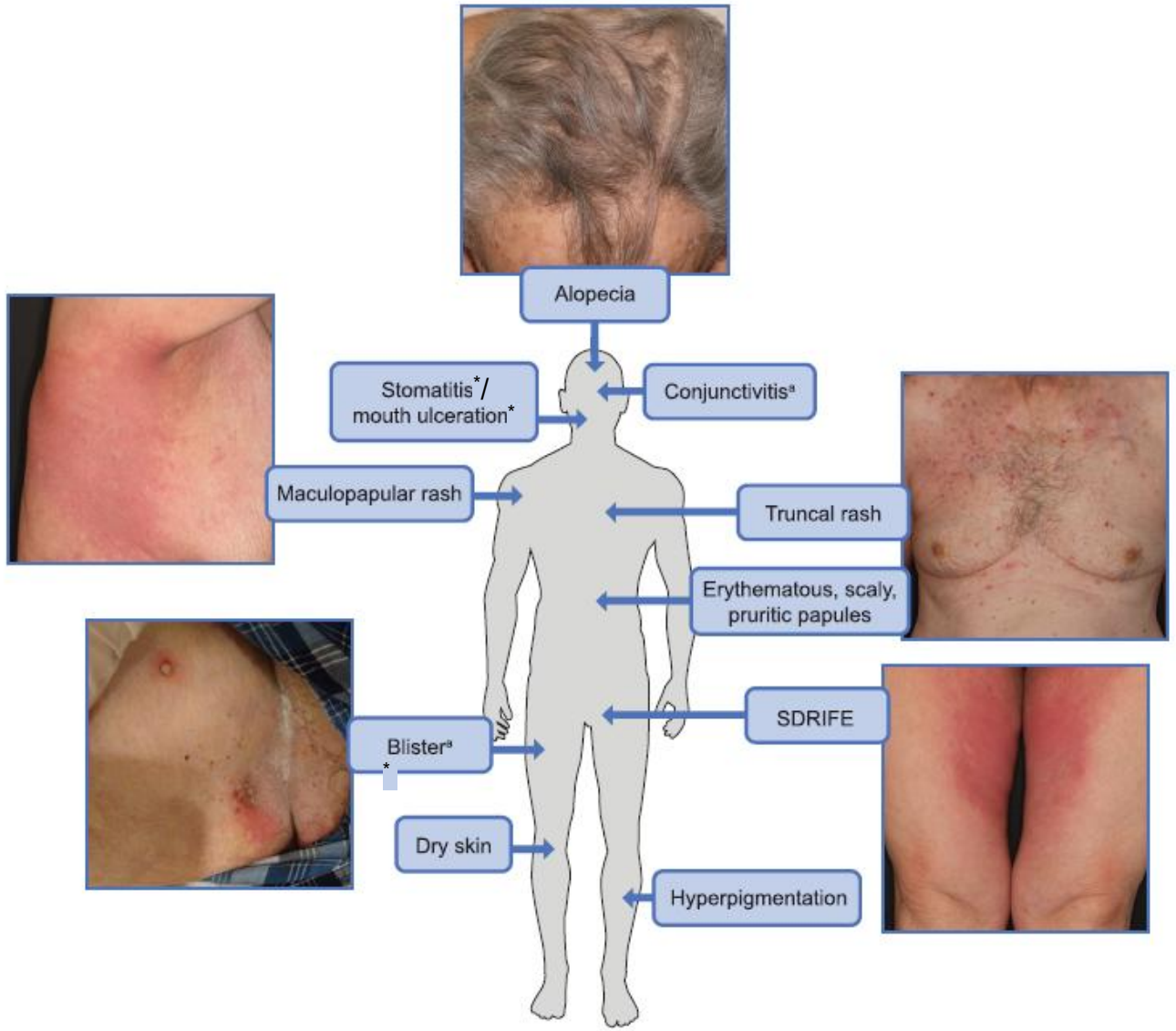
MMAE, monomethyl auristatin E.

Lacouture ME, et al. *Oncologist* 2022;27:e223-e232.

Selected dermatologic events associated with EV



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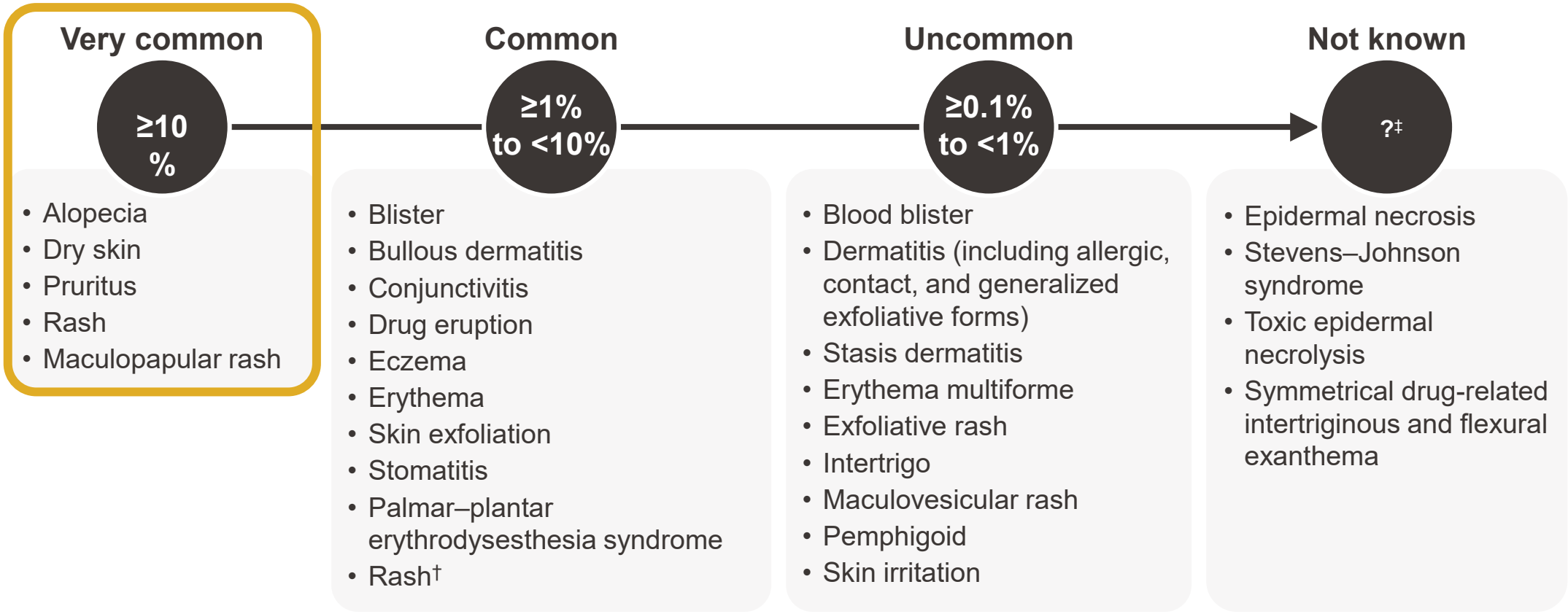
*Included in composite term for severe cutaneous adverse reactions based on standardized Medical Dictionary for Regulatory Activities query.

EV, enfortumab vedotin; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema.

Lacouture ME, et al. *Oncologist* 2022;27:e223-e232.

Common skin reactions associated with EV

Incidence of skin and subcutaneous tissue disorders associated with EV in clinical studies*



*Safety of EV monotherapy was evaluated in 680 patients with LA/mUC receiving EV 1.25 mg/kg; †Including erythematous, macular, papular, pruritic, and vesicular rash; ‡Based on global post-marketing experience.
EV, enfortumab vedotin; LA/mUC, locally advanced/metastatic urothelial carcinoma.
PADCEV™ (enfortumab vedotin). Summary of Product Characteristics;

EV-related skin reactions reported in EV-301

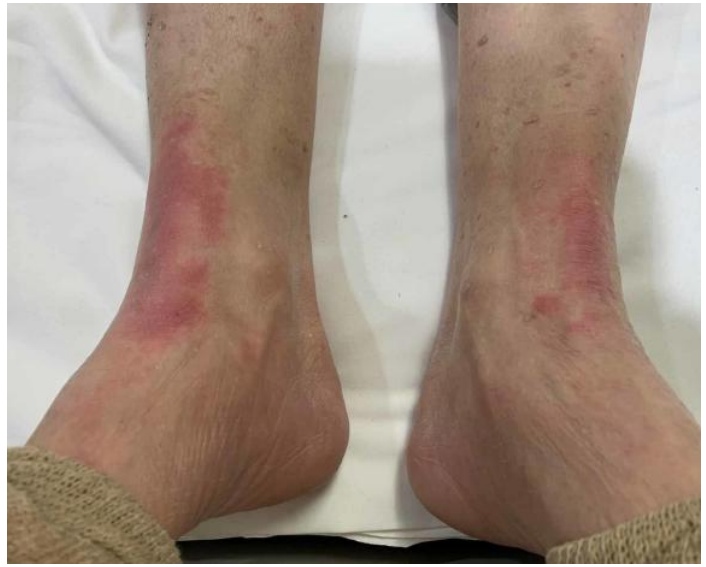
Skin reactions in EV-301 (N=296)	All grade, n (%)	Grade 3–4, n (%)
Any skin reaction	139 (47)	43 (15)
Any severe cutaneous adverse reaction*	60 (20)	15 (5)
Preferred term		
Rash maculopapular	48 (16)	22 (7)
Rash	45 (15)	5 (2)
Drug eruption	26 (9)	8 (3)
Stomatitis	21 (7)	1 (<1)
Conjunctivitis	9 (3)	1 (<1)
Rash erythematous	8 (3)	4 (1)
Skin exfoliation	7 (2)	1 (<1)
Dermatitis bullous	6 (2)	2 (1)
Erythema	6 (2)	1 (<1)
Blister	5 (2)	1 (<1)
Palmar-plantar erythrodysesthesia syndrome	3 (1)	0
Eczema	3 (1)	0
Rash macular	2 (1)	0
Rash pruritic	2 (1)	0
Rash vesicular	1 (<1)	1 (<1)
Perivascular dermatitis	1 (<1)	1 (<1)
Toxic skin eruption	1 (<1)	1 (<1)
Rash popular	1 (<1)	0
Erythema multiforme	1 (<1)	0
Exfoliative rash	1 (<1)	0
Dermatitis	1 (<1)	0
Fixed eruption	1 (<1)	0
Pemphigus	1 (<1)	0
Mouth ulceration	0	0

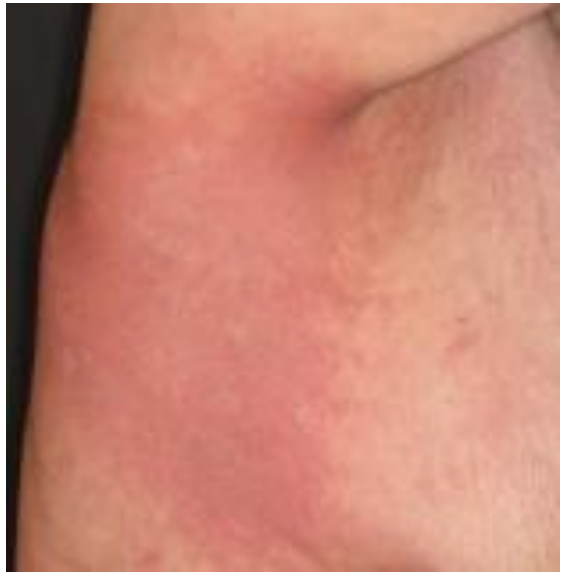
*Severe cutaneous adverse reactions were reported as a composite term of dermatologic and non-dermatologic events for based on standardized Medical Dictionary for Regulatory Activities v23.0 query.

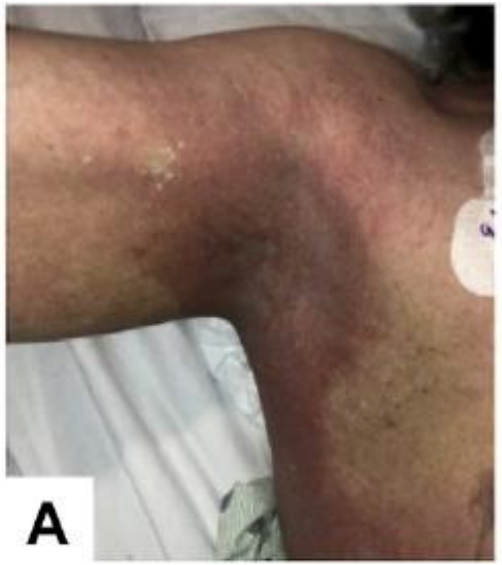
Lacouture ME, et al. *Oncologist*. 2022;27:e223–e232.

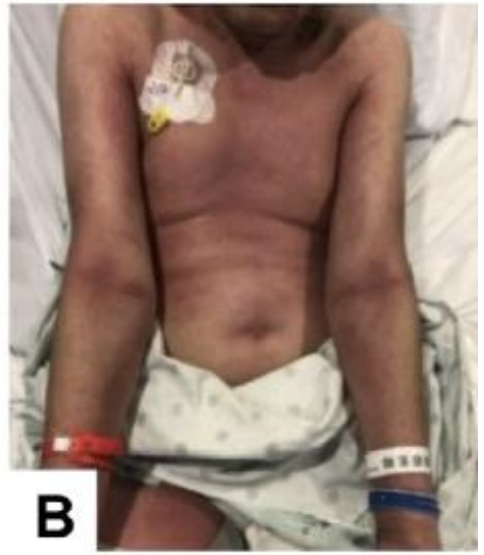
Maculopapular rash

- Erythematous macules, papules, patches, plaques[1–3]
- Often affecting the flexural, truncal or acral areas
- SDRIFE









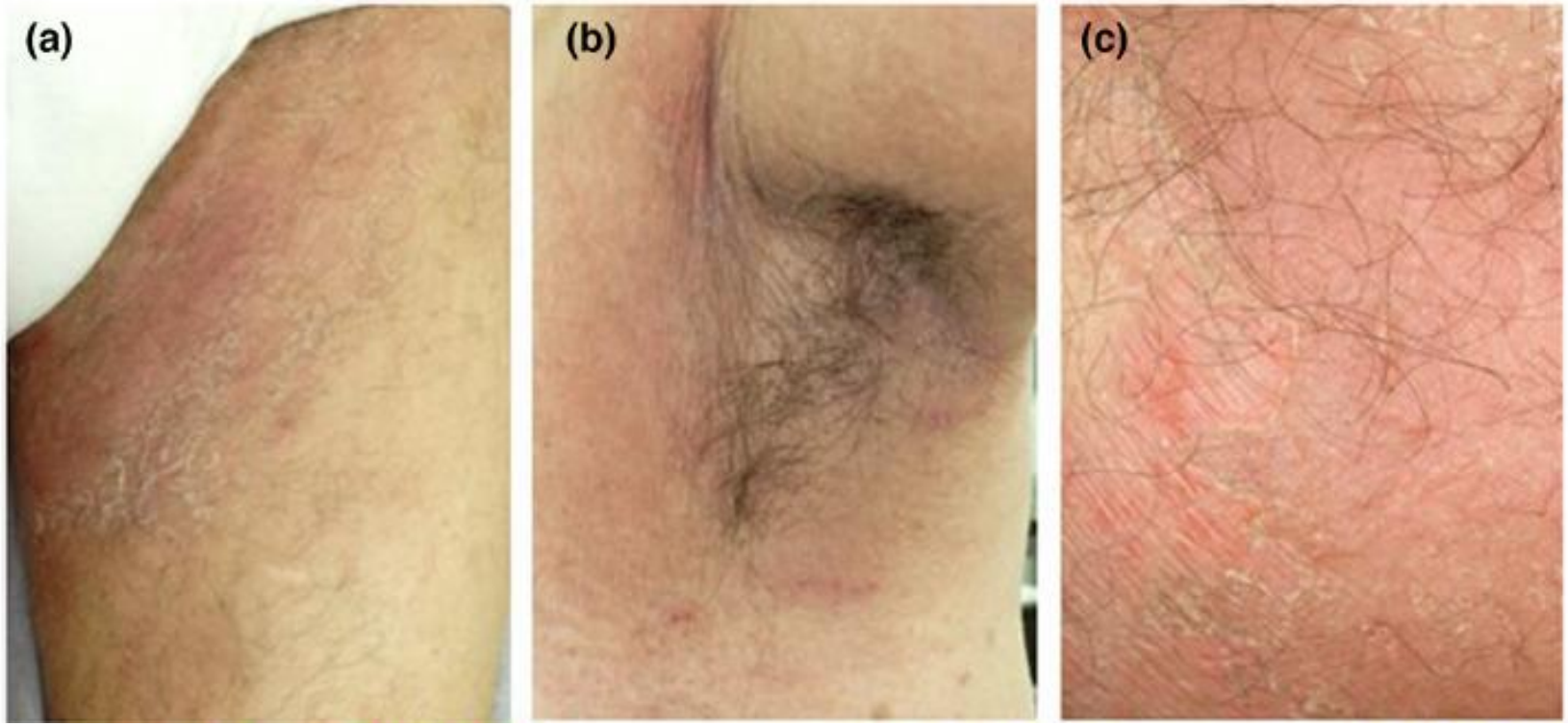
Images reproduced from 'Flexural Exanthema From Enfortumab Vedotin' Keerty D et al. *Cureus* 2020;12:e8102. Available at: Flexural Exanthema From Enfortumab Vedotin – PMC,[1] 'Management of Dermatologic Events Associated With the Nectin-4-directed Antibody-Drug Conjugate Enfortumab Vedotin' Lacouture ME et al. *Oncologist* 2022;27:e223–e232. Available at: https://academic.oup.com/oncolo/article/27/3/e223/6537593?login=false[2] and 'Clinical and Histopathological Characterization of Enfortumab Vedotin-Associated Cutaneous Toxicities: A Case Series' Egbeto IA, et al. *JAAD Case Resp* 2024;57:114–121. Available at: Clinical and histopathological characterization of enfortumab vedotin-associated cutaneous toxicities: A case series – PMC.[3] By CC: https://creativecommons.org/licenses/by-nc/4.0/

SDRIFE, symmetrical drug related intertriginous and flexural exanthem.

1. Keerty D, et al. *Cureus* 2020;12:e8102; 2. Lacouture ME, et al. *Oncologist* 2022;27:e223–e232; 3. Egbeto IA, et al. *JAAD Case Rep* 2024;57:114–121.

Desquamation

- Scaly, exfoliative appearance
- Eczematous, dermatitis

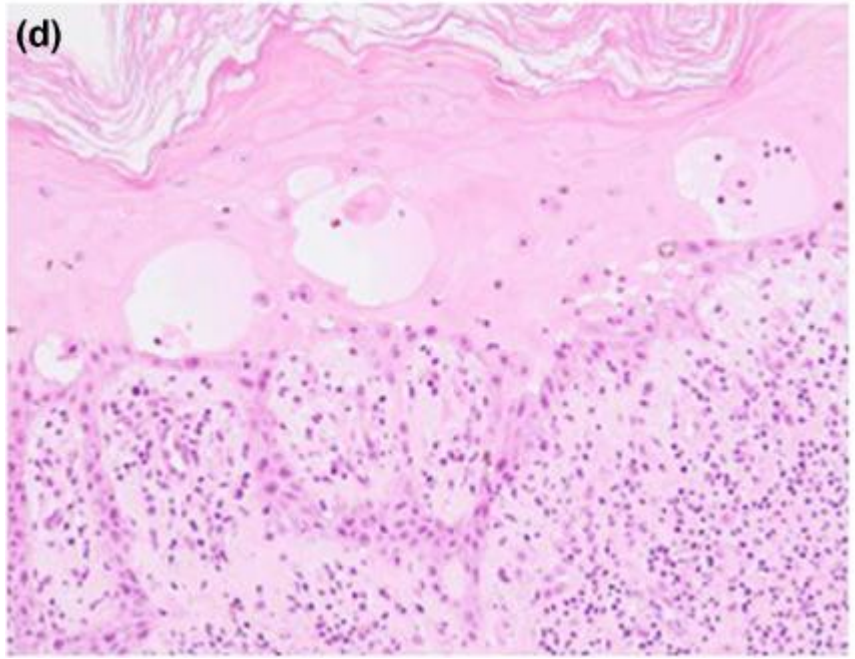


Images reproduced from 'Intertriginous erythema associated with enfortumab vedotin, a nectin-4-targeting antibody-drug conjugate, in a case with metastatic urothelial cancer: Immunohistochemical evidence for molecular-targeted eruption' Hasegawa T, et al. *J Dermatol* 2022;49:e453-e454. Available at: Intertriginous erythema associated with enfortumab vedotin, a nectin-4-targeting antibody-drug conjugate, in a case with metastatic urothelial cancer: Immunohistochemical evidence for molecular-targeted eruption - Hasegawa - 2022 - The Journal of Dermatology - Wiley Online Library.

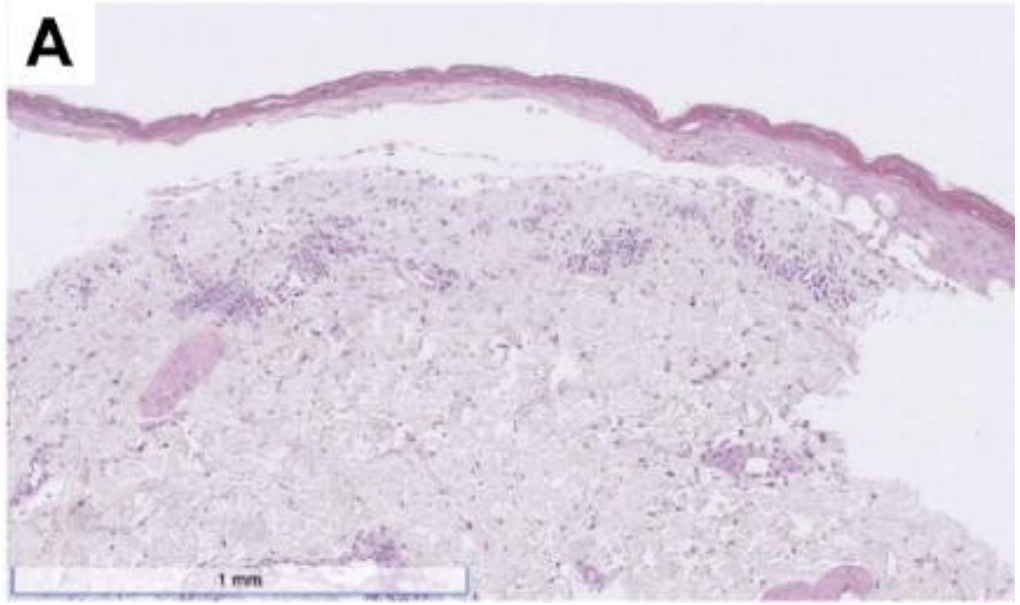
Hasegawa T, et al. *J Dermatol* 2022;49:e453-e454.

Histology

- Resembling “toxic erythema of chemotherapy”



Vesiculation and blisters with dyskeratotic cells in the entire epidermis, and perivascular lymphocytic infiltration in the dermis (d, ×100, HE)[1]



Subepidermal split[2]

Images reproduced from ‘Intertriginous erythema associated with enfortumab vedotin, a nectin-4-targeting antibody-drug conjugate, in a case with metastatic urothelial cancer: Immunohistochemical evidence for molecular-targeted eruption’ Hasegawa T, et al. *J Dermatol* 2022;49:e453-e454. Available at: Intertriginous erythema associated with enfortumab vedotin, a nectin-4-targeting antibody-drug conjugate, in a case with metastatic urothelial cancer: Immunohistochemical evidence for molecular-targeted eruption - Hasegawa - 2022 - The Journal of Dermatology - Wiley Online Library.[1] and ‘Clinical and Histopathological Characterization of Enfortumab Vedotin-Associated Cutaneous Toxicities: A Case Series’ Egbeto IA, et al. *JAAD Case Resp* 2024;57:114–121. Available at: Clinical and histopathological characterization of enfortumab vedotin-associated cutaneous toxicities: A case series – PMC.[2] By CC: https://creativecommons.org/licenses/by-nc/4.0/

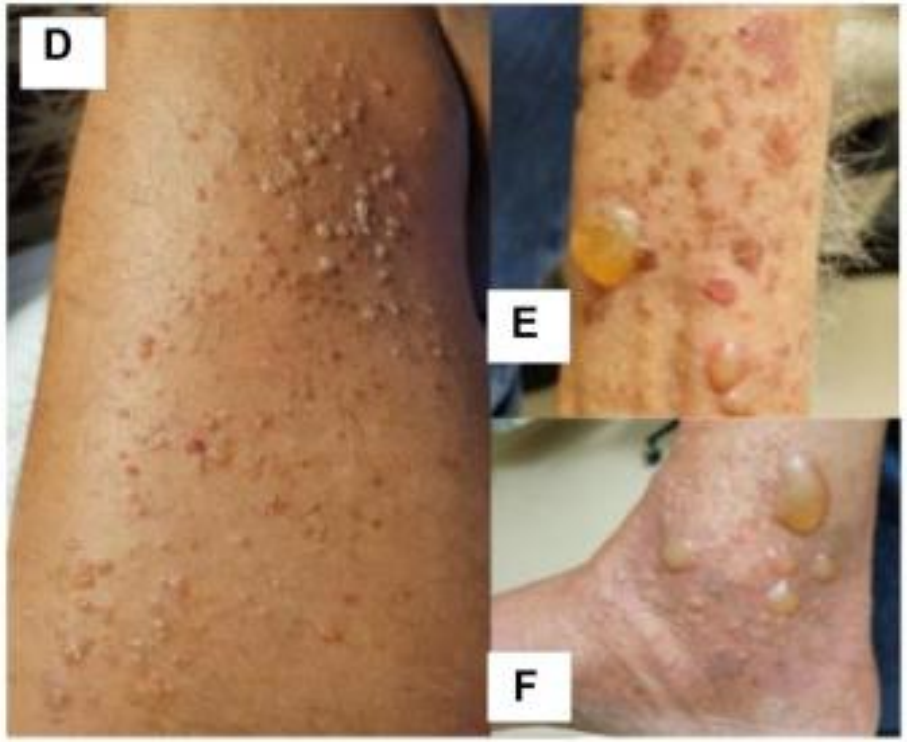
HE, hematoxylin and eosin.

1. Hasegawa T, et al. *J Dermatol* 2022;49:e453-e454; 2. Egbeto IA, et al. *JAAD Case Resp* 2024;57:114-121.

Blistering dermatosis

- Two cases: Latency of 6 weeks and 4 months[1]
- Histology: Interface dermatitis, intraepidermal blister and dyskeratotic keratinocytes, immunodeposits in the upper epidermis[1]
- Absence of serum skin autoantibodies[1]
- Suggesting an off-target delivery of MMAE → apoptosis of keratinocytes[1]

Representative images of blistering that can occur with EV+P[2]



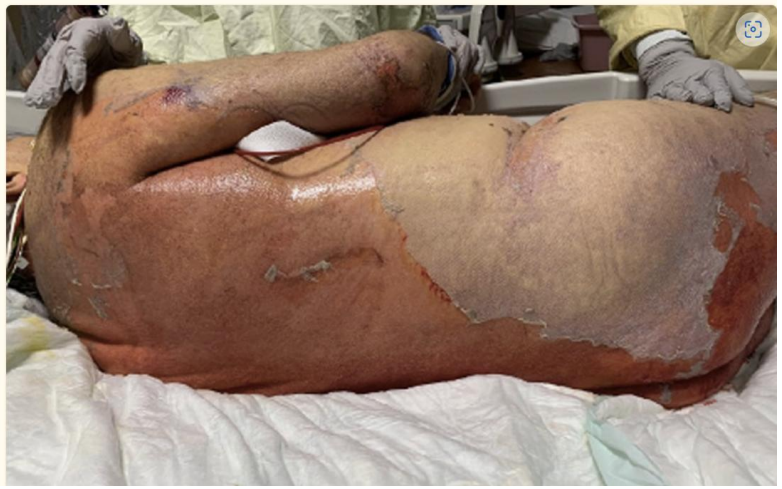
Images reproduced from 'Enfotumab vedotin therapy complicated by bullous dermatitis: A case report' Gillis MC et al. *JAAD Case Rep* 2025;56:40–44. Available at: Enfortumab vedotin therapy complicated by bullous dermatitis: A case report – ScienceDirect. By CC: https://creativecommons.org/licenses/by-nc/4.0/

MMAE, monomethyl auristatin E.

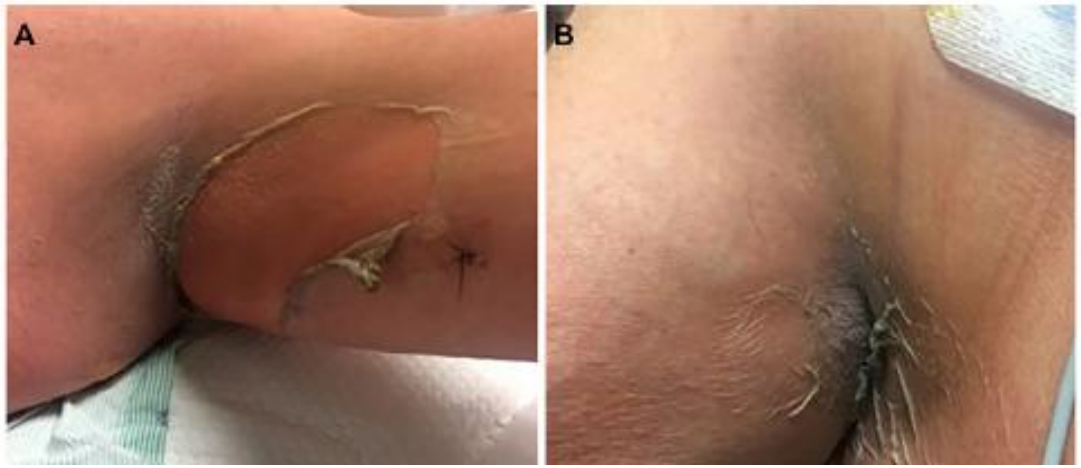
1. Penny C et al. *Br J Dermatol* 2022;187:126–132; 2. Gillis MC et al. *JAAD Case Rep* 2025;56:40–44.

SJS/TEN or SJS/TEN-like eruptions

- Few reports in literature



- After first cycle D8 infusion[1]
- More than 30% skin detachment with consistent histopathology[1]
- Deteriorated from event[1]

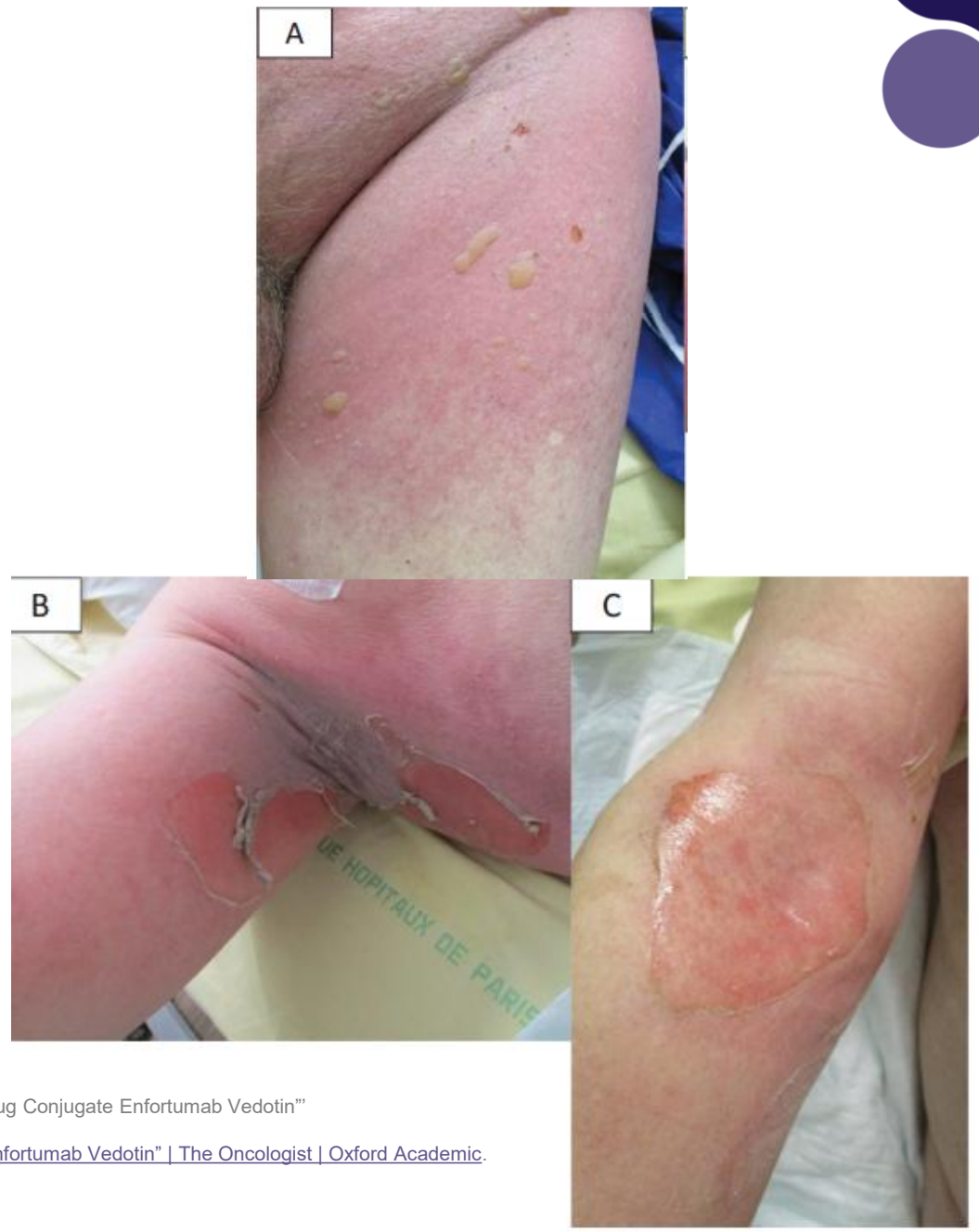


- Flexural skin denudation after third infusion[2]
- Had prior immunotherapy[2]

Images reproduced from 'A Rare Presentation f Enfortumab Vedotin-induced Toxic Epidermal Necrolysis' Francis A, et al. *JAAD Case Rep* 2020;7:57-59. Available at: A rare presentation of enfortumab vedotin–induced toxic epidermal necrolysis - JAAD Case Reports[1] and 'Case Report: Enfortuamb Vedotin for Metastatic Urothelial Carcinoma: A Case Series on the Clinical and Histopathologic Spectrum of Adverse Cutaneous Reactions from Fatal Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis to Dermal Hypersensitivity Reaction' Viscuse PV, et al. *Front Oncol* 2021;11:621591. Available at: Frontiers | Case Report: Enfortumab Vedotin for Metastatic Urothelial Carcinoma: A Case Series on the Clinical and Histopathologic Spectrum of Adverse Cutaneous Reactions From Fatal Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis to Dermal Hypersensitivity Reaction" By CC: https://creativecommons.org/licenses/by-nc/4.0/
SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
1. Francis A, et al. *JAAD Case Rep* 2020;7:57-59; 2. Viscuse PV, et al. *Front Oncol* 2021;11:621591.

SJS/TEN-like eruptions

- Median time to onset: 12–13 days
- Lack of/minimal mucosal involvement
- Detachment predominantly in large folds
- No diffuse dusky macules
- “EV-related flexural necrolysis” – likely due to direct skin toxicity rather than an immune-mediated mechanism in classic SJS/TEN
- Nonetheless, prognosis was poor – multiorgan failure



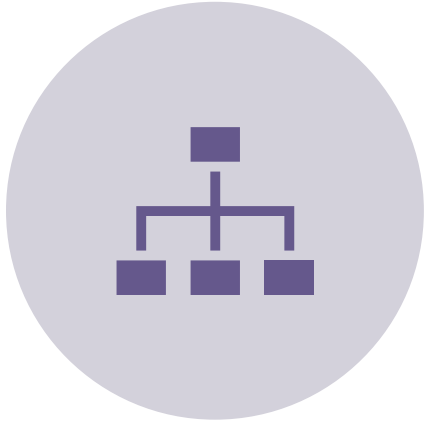
Images reproduced from ‘Regarding “Management of Dermatologic Events Associated with the Nectin-4-directected Antibody-Drug Conjugate Enfortumab Vedotin”’ Ingen-Housz-Oro S, et al. *Oncologist* 2022;27:e825–e826.
Available at: Regarding “Management of Dermatologic Events Associated with the Nectin-4–directed Antibody-Drug Conjugate Enfortumab Vedotin” | The Oncologist | Oxford Academic.

EV, enfortumab vedotin; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
Ingen-Housz-Oro S, et al. *Oncologist* 2022;27:e825–e826.

Management of cutaneous toxicities

1 PREVENTION

2 MONITORING



3 MANAGEMENT

1. Preventative care

- Emollients – barrier protection[1]
- Sun protection[1]
- Keep a cool environment[2]
- Treat any pre-existing skin conditions[1,2]

- Patient counselling[1,2]
- Expected cutaneous ADR[2]
- Red flags: Fever, mucosal involvement, skin pain/blistering[1]

Warning signs and symptoms of severe cutaneous adverse events, including SJS/TEN[1]

- **Malaise**
- **Fever ≥100.4°F**
- **Mucosal involvement**
  - **Ocular (conjunctivitis)**
  - **Oral**
  - **Genital**
- **Dermatodynia (skin pain, burning, numbness, or tingling)**

ADR, adverse drug reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

1. Lacouture ME, et al. *Oncologist* 2022;27:e223-e232; 2. Speaker's expert opinion.

General skincare

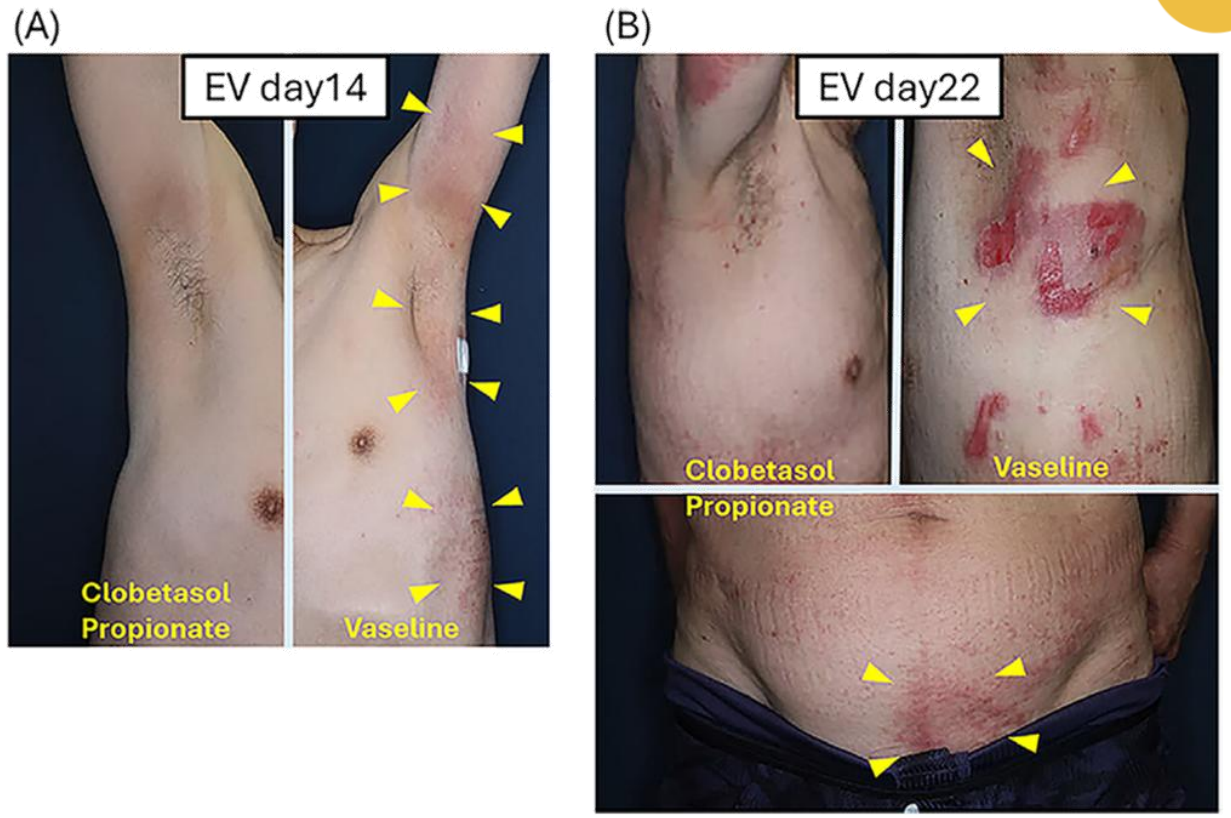
Cleansing	Moisturizing	Treatment	Sun protection
Bathe with lukewarm water Gentle soap-free cleansers	Use of fragrance-free moisturizing creams/ zinc-containing barrier creams	Topical treatments if needed	Use sunscreen SPF >30 broad spectrum, sun-protective clothing

SPF, sun protection factor.
Speaker's expert opinion.

Prophylactic steroids being studied: No definite role at present

Number of patients: 5	Flexural application of super-potent topical steroid clobetasol propionate vs. Vaseline
3 out 5 developed cutaneous AE on the Vaseline side only	No reported ADR
Median F/U 4.9 months	Plan for RCT

Caution: Risk of atrophy with use of super-potent topical treatments in flexural areas



Photographs of bilateral application sites in case KUEV03 (A) at the time of EVRCT onset and (B) highest EVRCT grade

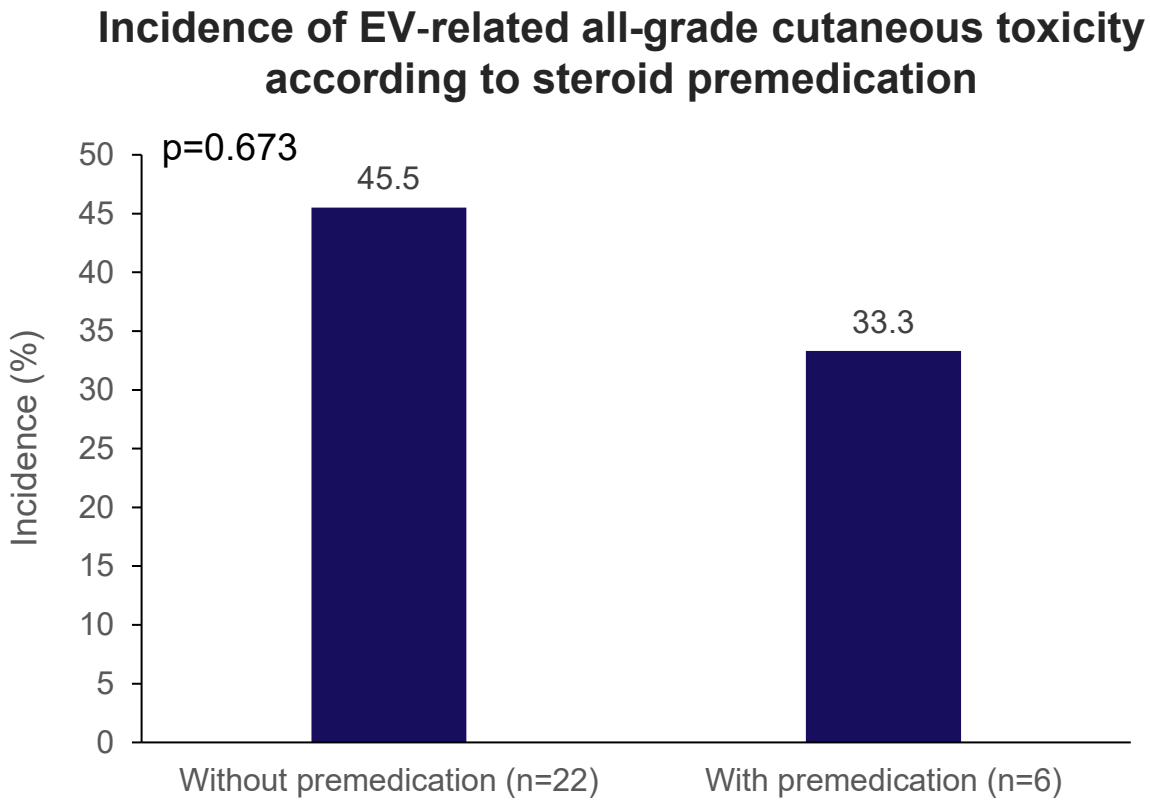
AE, adverse events; ADR, adverse drug reaction; EVRCT, EV-related cutaneous toxicity; F/U, follow-up; RCT, randomized controlled trial.

Prophylactic steroids being studied: No definite role at present

IN VIVO 39: 1607-1614 (2025)
doi: 10.21873/invivo.13961

Steroid Premedication Impact on Efficacy and Cutaneous Toxicity of Enfortumab Vedotin for Advanced Urothelial Carcinoma

- N=28
- IV dexamethasone 6.6 mg
- No difference in incidence of all cutaneous AEs and high-grade (Grade ≥3) AEs
- No difference in overall response



AE, adverse event; EV, enfortumab vedotin
Furubayashi N, et al. *In Vivo* 2025;39:1607–1614.

2. Monitoring

- At each visit/prior to infusion, particularly in the first 1–2 cycles

Complete **visual skin inspection** and **palpation**[1,2]

Use a **grading system** (e.g., CTCAE) to standardise **assessment of the skin**[2]

Record and photograph the colour, texture, morphology, distribution, and extent of any **lesions**[2]

Monitor the skin for **secondary skin infections**[1]

Assess for the presence of **additional symptoms** (e.g., fever, malaise)[2] – fever or flu-like symptoms may be the **first sign** of a severe skin reaction[3]

Consider whether prior treatments such as CPIs may cause priming or residual toxicity [4–6]

CPI, checkpoint inhibitor; CTCAE, Common Terminology Criteria for Adverse Events; EV, enfortumab vedotin.

1. Pace A et al. *Clin J Oncol Nurs* 2021;25:E1–E9; 2. Barton-Burke M et al. *Nurs Clin North Am* 2017;52:83–113; 3. PADCEV™ [prescribing information]. Northbrook, IL: Astellas Pharma US, Inc.;
4. Tattersall IW & Leventhal JS. *Yale J Biol Med* 2020;93:123–132; 5. Dobry AS et al. *JAAD Case Rep* 2021;14:7–9; 6. Lacouture ME et al. *Oncologist* 2022;27:e223–e232.

3. Management: General principles

Treat cutaneous AEs to allow continuation of treatment[1]

Management considerations:[2]

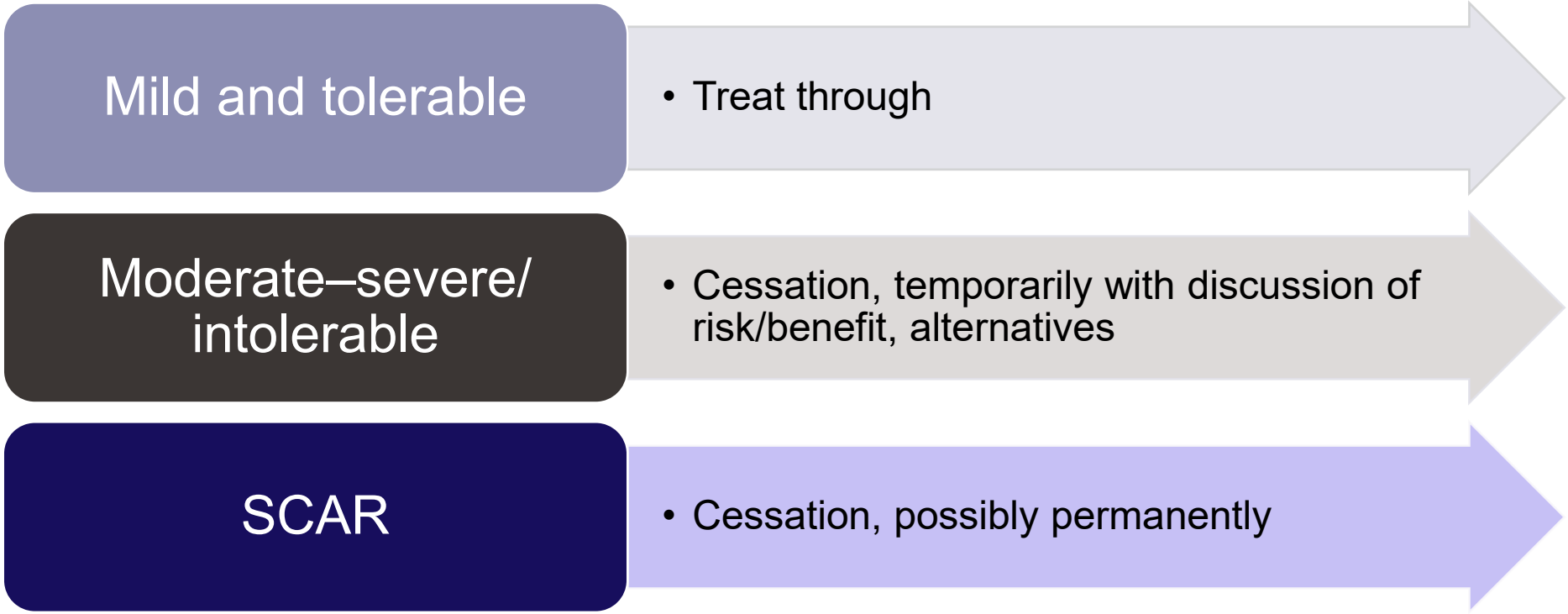
- What kind of reaction?
- How severe? CTCAE Grade & impact on QOL
- Are there good alternatives?

Close collaboration between the oncologist and dermatologist[1]

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; QOL, quality of life.

1. Pace A et al. *Clin J Oncol Nurs* 2021;25:E1–E9; 2. Barton-Burke M et al. *Nurs Clin North Am* 2017;52:83–113.

Management: General principles



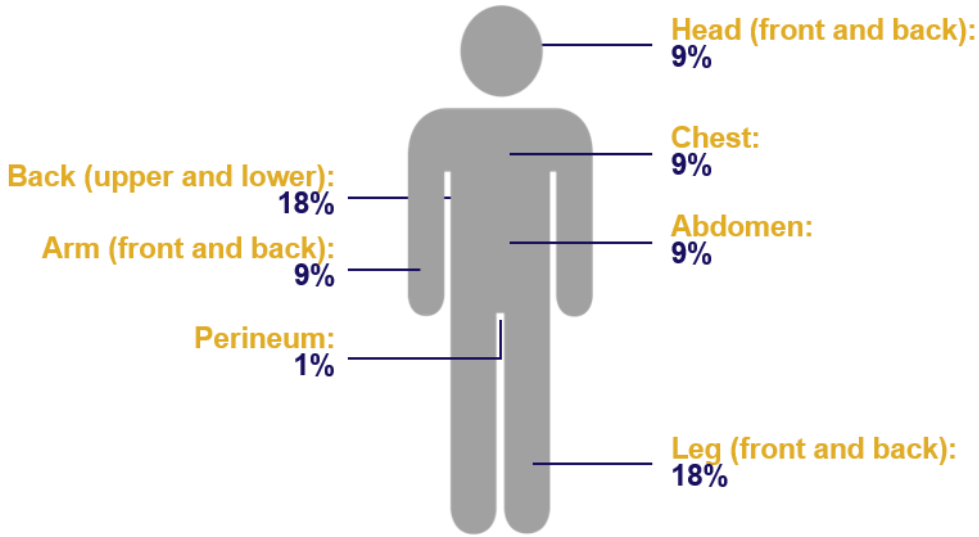
SCAR, severe cutaneous adverse reaction.
Speaker's expert opinion.

Assessing severity: CTCAE

Considerations:[1,2]

- Morphology of rash
- BSA used to assess the severity of skin reactions such as SJS, TEN and maculopapular rash
  - BSA can be calculated using the 'rule of nines'
- Symptoms
- Impact on iADL and self-care ADL

Guide to estimating percentage BSA for a typical adult patient, by region[2]



Grading of maculopapular rash according to CTCAE v5.0[1]

Grade 1	Grade 2	Grade 3
• <10% BSA ± symptoms	• 10–30% BSA ± symptoms limiting iADL • >30% BSA ± mild symptoms	• >30% BSA with moderate or severe symptoms, limiting ADL

BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; (i)ADL, (instrumental) activities of daily living; SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrolysis.

1. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Last accessed: July 2025; 2. Barton-Burke M, et al. *Nurs Clin North Am* 2017;52:83-113.

Blistering dermatosis: Severity grading

Bullous dermatitis

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
• <10% BSA • Asymptomatic	• 10–30% BSA • Painful, limiting iADL	• >30% BSA • Limiting self-care ADL	• >30% BSA • Fluid/electrolyte abnormalities, burns/ICU indicated	• Death

SJS/TEN

Grade 3	Grade 4	Grade 5
• <10% BSA • Mucosal	• >10% BSA • Mucosal	• Death

BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; (i)ADL, (instrumental) activities of daily living; ICU, intensive care unit; SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrolysis.

US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Last accessed: July 2025

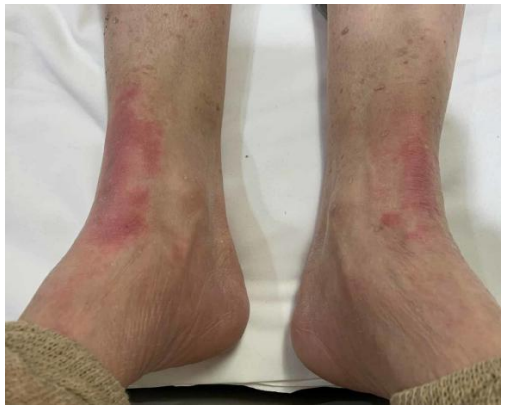
Grade 1

<10% BSA[1]

Management:[2]

- Topical corticosteroids
- Antihistamines and emollients
- Can usually continue treatment

Bilateral flexural exanthema of feet[3]



Treatment[4]		
Potency	**Location**	**Examples**
Low	Face/flexures	Hydrocortisone 1% cream Betamethasone valerate 0.025% cream Desonide cream
Moderate	Body/Limbs	Betamethasone valerate 0.1% cream Mometasone cream
Potent	Palms/Soles	Betamethasone dipropionate Clobetasol propionate

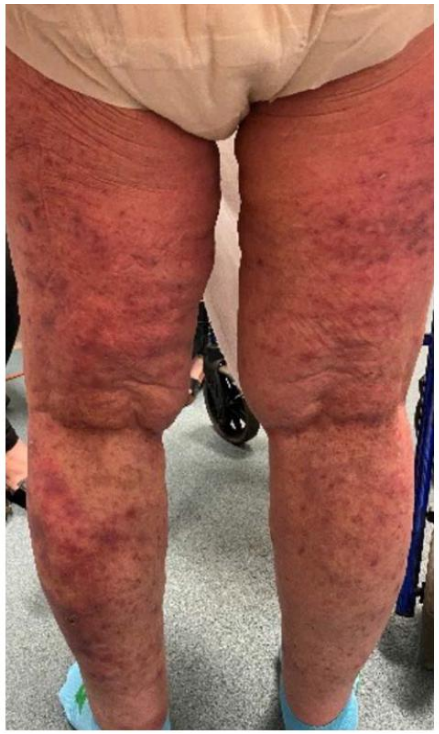
Image reproduced from 'Flexural Exanthema From Enfortumab Vedotin' Keerty D et al. *Cureus* 2020;12:e8102. Available at: Flexural Exanthema From Enfortumab Vedotin – PMC, By CC: https://creativecommons.org/licenses/by-nc/4.0/
BSA, body surface area.
1. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Last accessed: July 2025; 2. Lacouture ME, et al. *Oncologist* 2022;27:e223–e232; 3. Keerty D, et al. *Cureus* 2020;12:e8102; 4. Speaker's expert opinion.

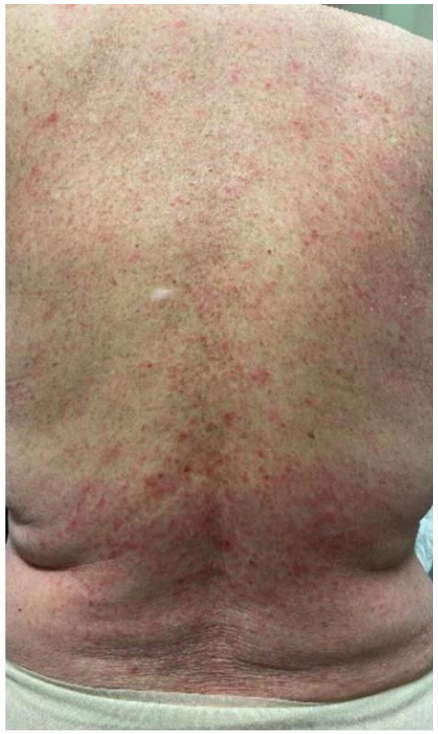
Grade 2

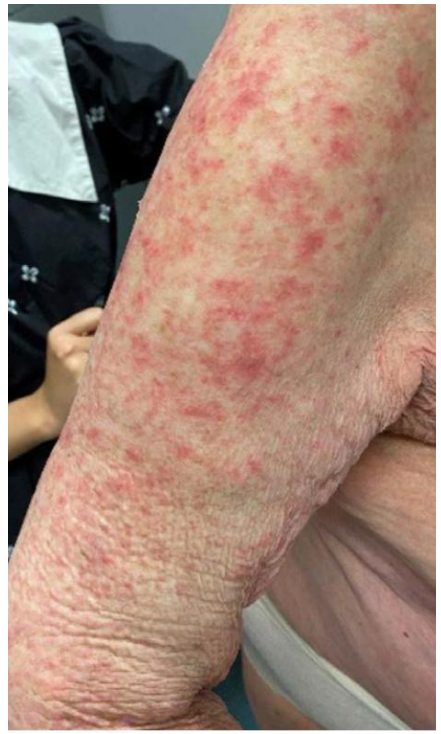
10–30% BSA[1]

Management:

- Topical corticosteroids[2]
- Treat any concomitant bacterial/fungal infection[2]
- If intolerable or symptoms appear or are progressive:[3]
  - Temporary treatment cessation may be needed
  - Systemic corticosteroids may be considered
  - Consider dermatology referral







BSA, body surface area.

1. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Last accessed: July 2025; 2. Lacouture ME, et al. *Oncologist* 2022;27:e223–e232; 3. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

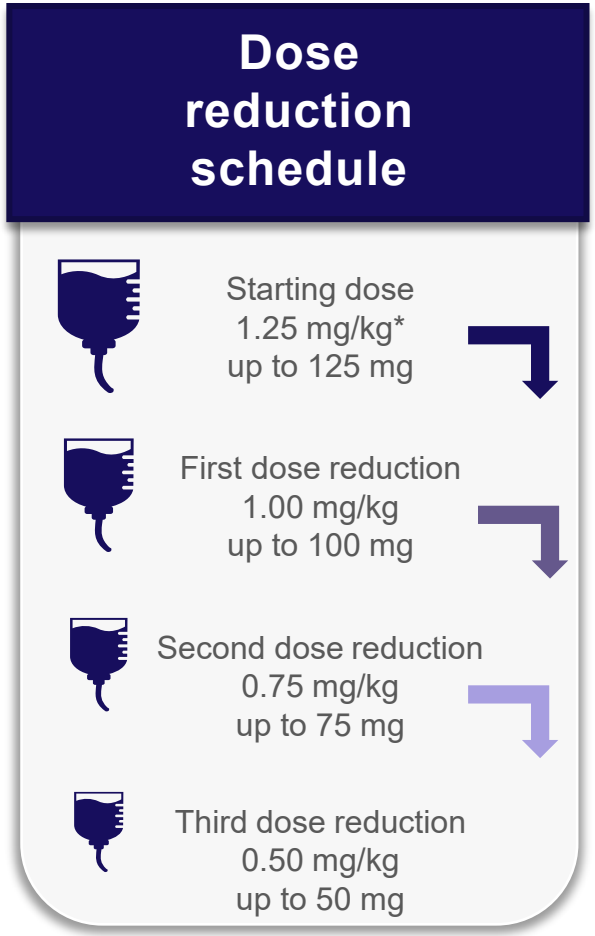
Grade 3

>30% BSA[1]

Management:[2,3]

- Temporary interruption of treatment
- Consider dermatology referral
- Consider oral corticosteroids e.g., prednisone 0.5 mg/kg/day (tailing off after approximately 2 weeks)
- If improves to Grade 1, consider restarting treatment at the same dose level or consider dose reduction by one level

Recommended EV dose reduction schedule[4]



*Up to a maximum of 125 mg for patients weighing ≥100 kg.
BSA, body surface area.

1. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Last accessed: July 2025; 2. Lacouture ME, et al. *Oncologist* 2022;27:e223–e232; 3, Speaker's expert opinion; 4. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

Grade 4 or suspected SJS/TEN

Management:[1,2]

- Refer to dermatologist urgently
- May require admission for monitoring and treatment
- Skin biopsy for diagnosis and exclusion of DDx
- Discontinue treatment

DDx, differential diagnosis; SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrolysis.

1. Lacouture ME, et al. *Oncologist* 2022;27:e223–e232; 2. Speaker's expert opinion.

Note on blistering reactions

Includes bullous dermatitis, erythema multiforme, any suspected case of SJS/TEN. Usually treated more seriously because of risk of progression to more widespread blistering/severe cutaneous adverse reactions need to be ruled out[1,2]

Low threshold for dermatology referral[1,2]

Skin biopsy for histology and direct immunofluorescence usually indicated to rule out:[2]

- SJS/TEN
- Autoimmune blistering disease

In widespread blistering, admission may be needed for supportive management[2]

- Wound care with non-adherent dressings
- Prevention of infection
- Fluid/electrolyte support

SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrolysis.

1. Speaker's expert opinion; 2. Lacouture ME, et al. *Oncologist* 2022;27:e223–e232.

Management of non-SJS/TEN blistering

Grade 1: BSA <10%[1]

- Topical corticosteroids + antibiotic combinations e.g., betamethasone + fusidic acid[2]
- Consider drug cessation (temporary) to allow skin healing[3]
- Blister care:[3]
  - Prick and decompress, do not deroof
  - Potassium permanganate compresses
  - Topical treatment
  - Non-adhesive dressing

Grade 2 and above: BSA >10%[1]

- Add systemic corticosteroids[2]
- Consider admission for skin and supportive care[3]

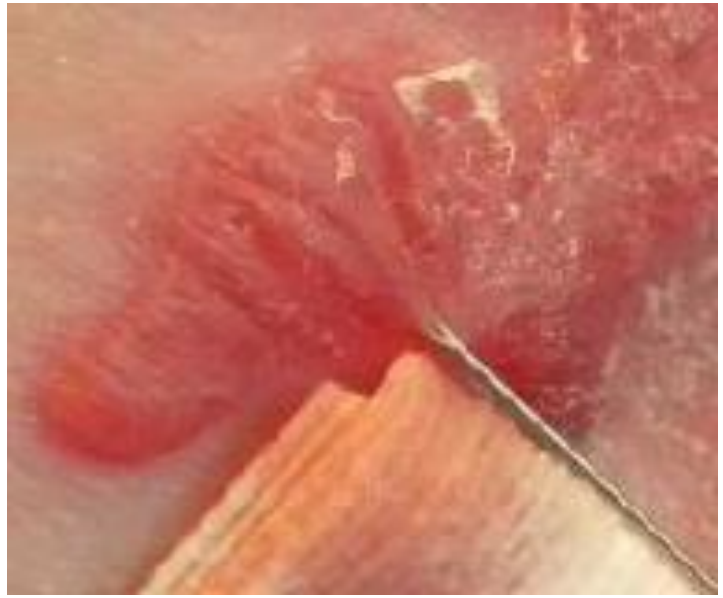


Image provided by the speaker with permissions.
BSA, body surface area; SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrolysis.
1. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Last accessed: July 2025; 2. Lacouture ME, et al. *Oncologist* 2022;27:e223–e232; 3. Speaker's expert opinion.

Management of skin reactions to EV

Management of skin reactions to EV per SmPC*

Management strategy	Grade 1 (mild)	Grade 2 (moderate)		Grade 3 (severe)		Grade 4 (life-threatening)
		Stable/no fever	Worsening/fever	First event	Recurrent event	
EV dose modification	None[1]		**Withhold EV until Grade ≤1** then **resume** at the same/one level lower dose[1]		**Permanently discontinue EV**[1]	
Pharmacological interventions	If indicated: Topical **corticosteroids**, topical **antibiotics**, topical/oral **antihistamines**[1–3†]			Treat with **systemic corticosteroids**[2,3‡]		
	Consider **creams/ emollients**[2,3]	Consider **anti-infective agents**[3]				
Referral	None[1]		Consider **dermatologist referral**[1]			
					Admit to hospital for specialised care[3]	

Maculopapular rash and pruritis can be defined as Grade 1, 2, or 3[4]

For suspected SJS, TEN, or bullous lesions, immediately withhold EV and refer to specialised care[1]

*Grading according to CTCAE.[2]
†For example, a combination of moderate-potency topical corticosteroid (e.g., triamcinolone 0.1% cream) and topical antibiotic (e.g., silver sulfadiazine 1% cream) may be used.[3]
‡For example, prednisone 0.5 mg/kg/day (or equivalent) for 14 days.[3]
CTCAE, Common Terminology Criteria for Adverse Events; EV, enfortumab vedotin; SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrolysis.
1. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 2. Pace A, et al. *Clin J Oncol Nurs* 2021;25:E1–E9; 3. Lacouture ME, et al. *Oncologist* 2022;27:e223–e232; 4. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Last accessed: July 2025.

Genitourinary Masterclass

astellas

Treatment outcomes of cutaneous AEs

AE, adverse event.

Outcomes in EV-301

Dose reduction: 8%

Skin reactions leading to dose reduction of EV (N=296)	n (%)
Any skin reaction	24 (8)
Any severe cutaneous adverse reaction*	5 (2)
Preferred term	
Rash maculopapular	13 (4)
Rash erythematous	1 (<1)
Rash vesicular	1 (<1)
Drug eruption*	4 (1)
Rash	3 (1)
Stomatitis*	1 (<1)
Eczema	1 (<1)
Erythema	1 (<1)
Perivascular dermatitis	1 (<1)

Treatment withdrawal: 4%

Skin reactions leading to treatment withdrawal of EV (N=296)	n (%)
Any skin reaction	12 (4)
Any severe cutaneous adverse reaction*	6 (2)
Preferred term	
Rash maculopapular	4 (1)
Drug eruption*	2 (1)
Dermatitis bullous*	2 (1)
Rash	1 (<1)
Rash erythematous	1 (<1)
Conjunctivitis*	1 (<1)
Toxic skin eruption*	1 (<1)

Dose interruption: 11%

Skin reactions leading to dose interruption of EV (N=296)	n (%)
Any skin reaction	33 (11)
Any severe cutaneous adverse reaction*	14 (5)
Preferred term	
Rash maculopapular	13 (4)
Rash	10 (3)
Rash erythematous	1 (<1)
Drug eruption*	7 (2)
Dermatitis bullous*	3 (1)
Dermatitis acneiform	2 (1)
Blister*	1 (<1)
Conjunctivitis*	1 (<1)
Fixed eruption*	1 (<1)
Skin exfoliation*	1 (<1)
Stomatitis*	1 (<1)

*Severe cutaneous adverse reactions were reported as a composite term of dermatologic and non-dermatologic events for based on standardized Medical Dictionary for Regulatory Activities v23.0 query.
EV, enfortumab vedotin.
Lacouture ME, et al. *Oncologist*. 2022;27:e223–e232.

Prognosis

- In many cases, short duration of cessation may be sufficient due to the short half-life of EV
- Once AEs are at Grade ≤1, you may restart at the same dose, or reduce by one dose level
- Among the 59 patients in the integrated safety population who experienced a skin reaction requiring dose interruption and who then restarted EV treatment:
  - 24% of those who restarted at the same dose experienced a recurrence of severe skin reaction
  - 16% of those who restarted at a lower dose experience a recurrence of severe skin reaction
- Despite the high rate of cutaneous AEs, treatment cessation due to cutaneous AEs is low

AE, adverse event; EV, enfortumab vedotin.

Lacouture ME, et al. *Oncologist*. 2022;27:e223–e232.

Outcomes

- N=58, Mayo
- A total of 15/58 (25.86%) developed CAE
- Mean onset: 19.9 days (range 7–63 days)
- Median number of treatment cycles: 1 (range 1–3)
- 60% of patients continued at the same dose
- 26% of patients required dose reduction
- 13.3% of patients discontinued EV therapy
- Of those who continued at the same dose:
  - Rash persistence: 46.7%
  - Rash resolution: 40%

Treatment regimen for cutaneous adverse events	
	Total (N=15)
Treatment, n (%)	
Betamethasone cream	2 (13.3)
Triamcinolone cream	3 (20)
Hydrocortisone 2.5% cream	6 (40)
Prednisone 5 mg	1 (6.7)
Prednisone 10 mg	1 (6.7)
Prednisone 20–40 mg	1 (6.7)
Oral antihistamines	7 (46)
Clindamycin lotion	1 (6.7)
Treatment duration, weeks	
N (missing)	13 (2)
Mean (SD)	14.1 (13.8)
Range	1.0–41.0
Treatment response, n (%)	
Complete	6 (60.0)
N/A	2 (13.3)
Partial	3 (20.0)
Stable	1 (6.7)

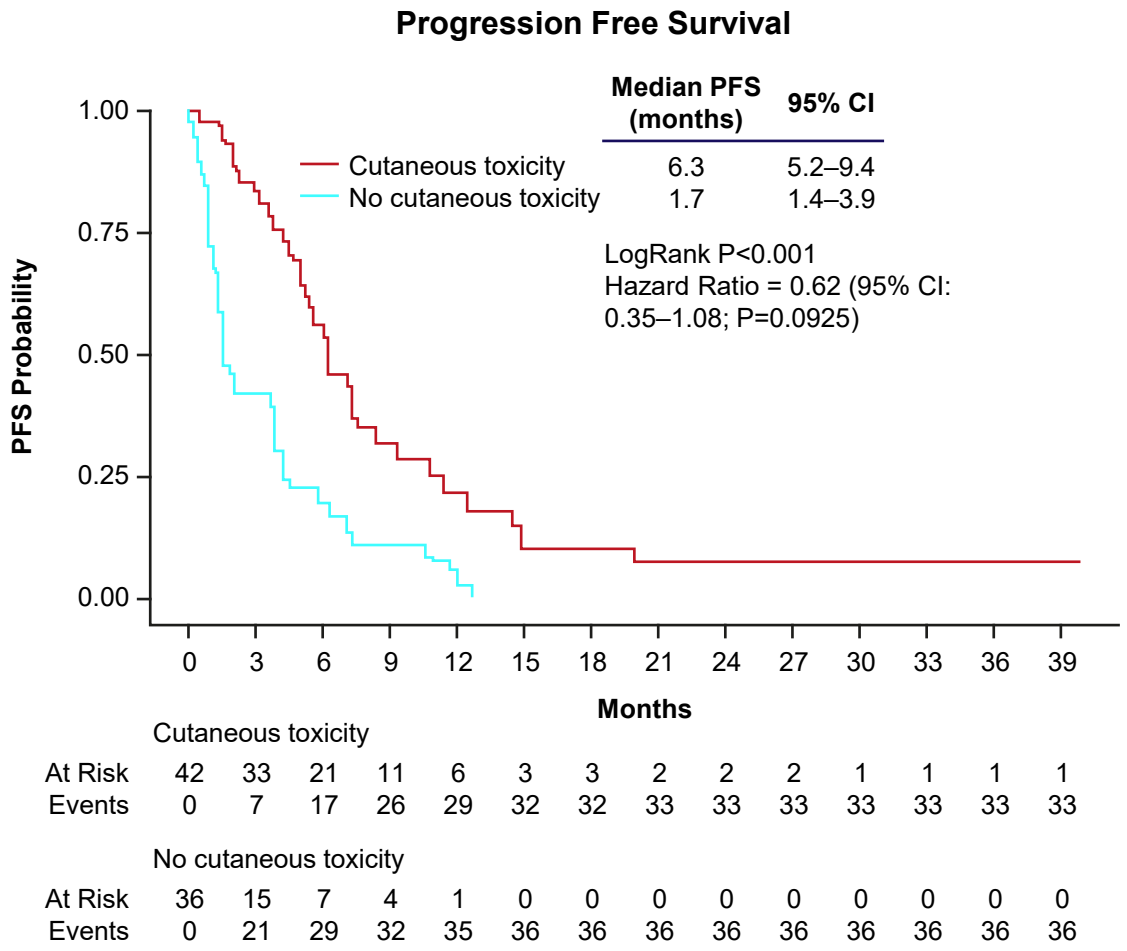
CAE, cutaneous adverse event; EV, enfortumab vedotin; N/A, not applicable; SD, standard deviation.
Shahin A et al. *JAAD Int* 2023;10:46–47.

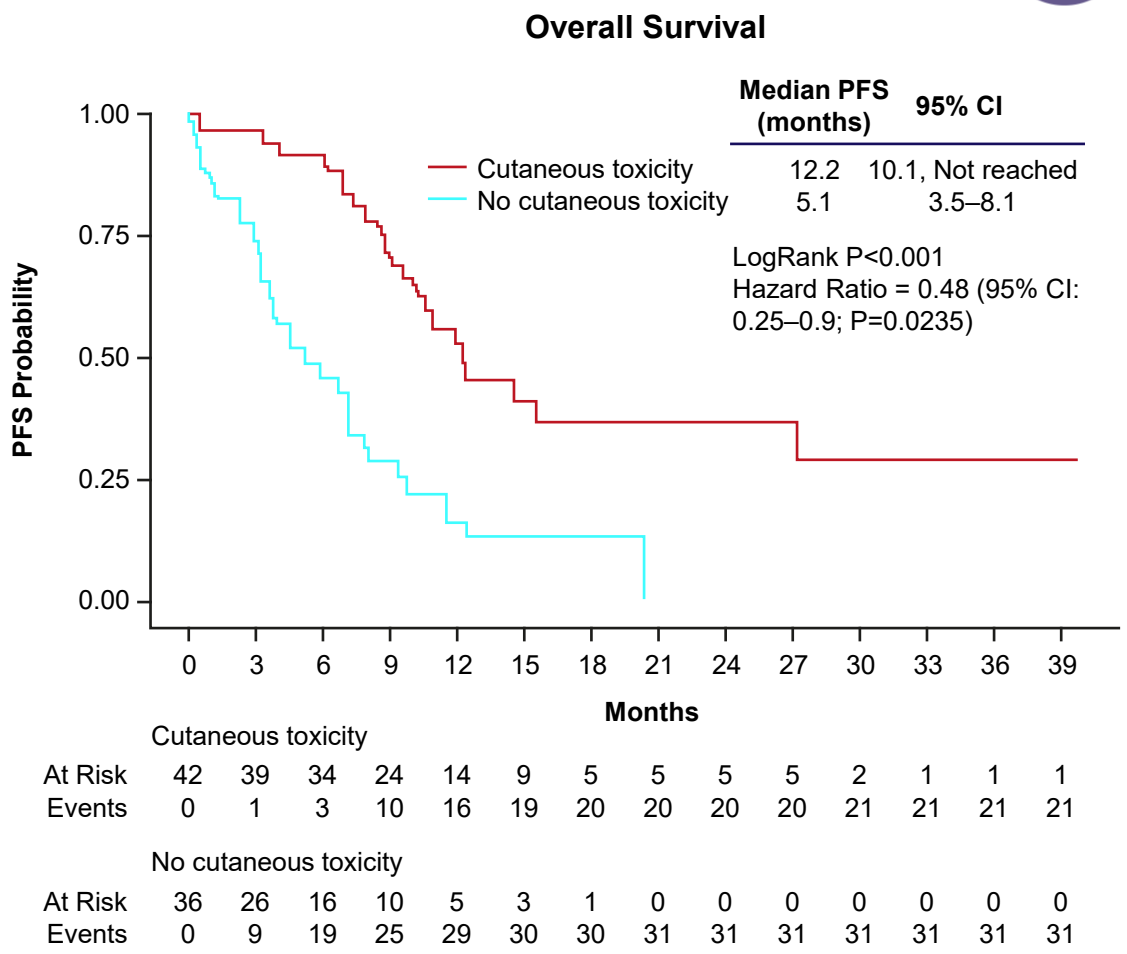
Prognosis: Bullous dermatitis due to EV

- Both were Grade 2 reactions and treatment was temporarily stopped
- Case 1: Resolved with prednisone, challenged with recurrence and required prednisone
  10 mg to prevent recurrence, eventually stopped due to liver failure
- Case 2: Able to tolerate EV at reduced dosage with mild intermittent rash

EV, enfortumab vedotin.
Penny C et al. *Br J Dermatol* 2022;187:126–132

Prognosis





This information has not been validated through pivotal or large-scale studies, however small studies have suggested an association between cutaneous toxicities and improved survival*

***Disclaimer: This information has not been validated through pivotal or large-scale studies. Data are included here as part of the speaker's personal scientific opinion.**

CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Vlachou E, et al. *Front Oncol* 2024;14:1377842.

Summary

- Most skin reactions are **mild and transient, occur early**[1] and are manageable through dose reduction or interruption[2]
- **Optimal and early management** of skin side effects can allow continuation of treatment in many cases[3-5]
- If blisters are observed, or SJS/TEN is suspected, **immediately withhold EV and consider a dermatology referral**[6]
- Patients should be **educated** about the **symptoms** of skin reactions and the **importance of prompt reporting and management**[4]
- **AE management and dose modification guidance** can be used by HCPs to effectively manage AEs associated with EV such as skin toxicities[6]

AE, adverse event; EV, enfortumab vedotin; HCP, healthcare professional; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

1. Powles T et al. *N Engl J Med* 2021;384:1125–1135; 2. Powles T et al. *N Engl J Med* 2021;384:1125–1135 (supplementary appendix). 3. Lacouture ME et al. *Oncologist* 2022;27:e223–e232; 4. Pace A et al. *Clin J Oncol Nurs* 2021;25:E1–E9; 5. Dobry A et al. *JAAD Case Rep* 2021;14:7–9; 6. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

Thank You!

Email: yeo.yi.wei@singhealth.com.sg

Management of Dermatologic Events Associated With the Nectin-4-directed Antibody-Drug Conjugate Enfortumab Vedotin

Lacouture ME, et al. *Oncologist* 2022;27:e223-e232.

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Principals of AE management with standard of care: Ask the experts

All Faculty

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Genitourinary Masterclass

Principles of AE management

Dr Niara Oliveira

Mater Hospital, Brisbane, Australia

EV as first-line therapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer. Combination therapy with pembrolizumab.

EV as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed death receptor-1 or programmed death-ligand 1 inhibitor, and have received a platinum-containing chemotherapy

1L, first line; EV, enfortumab vedotin;
LA/mUC, locally advanced/metastatic urothelial carcinoma; P, pembrolizumab;
PD-1/L1, programmed cell death-1/ligand 1.
PADCEV® (enfortumab vedotin). Prescribing Information
July 2025 | MAT-KR-PAD-2025-00076

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Take-home messages

Close monitoring for AEs during treatment with EV is important[1]

Early identification and effective care can help ensure patients are able to continue to receive their treatment, to ensure patients receive optimal treatment outcomes[1]

Patients continue to benefit from EV monotherapy even when dose modifications are required to manage AEs[2]

AE, adverse event; EV, enfotumab vedotin.

1. Brower B et al. *Front Oncol* 2024;14:1326715; 2. Petrylak D et al. Presented at ASCO 2024. Abstract 4503.

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