Consensus Guidance on Early Identification and Management of Peripheral Neuropathy in Patients With Urothelial Carcinoma Receiving Enfortumab Vedotin: A Delphi Study

Alexandra Drakaki,[1] Matthew Kurian,[2] Nataliya Mar,[3] Manoj Bupathi,[4] Amanda Nizam,[5] Hiba Ahmad,[6] Rick Bangs,[7] Ashley Aaroe,[8] Ali Habib,[3] Jennifer Lloyd,[9,10] Christian Custodio,[11] David Decewicz,[12] Michael Harrison,[13] Anasheh Halabi[1]

[1]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA; [2]St. Elizabeth Healthcare Cancer Center, Edgewood, KY, USA; [3]University of California Irvine, Orange, CA, USA; [4]Rocky Mountain Cancer Centers, Littleton, CO, USA; [5]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [6]University of Colorado Hospital, Anschutz Cancer Center, Aurora, CO, USA; [7]Bladder Cancer Advocacy Network, Pittsford, NY, USA; [8]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [9]College of Nursing, University of Utah, Salt Lake City, UT, USA; [10]Intermountain Health, Murray, UT, USA; [11]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [12]Astellas Pharma Inc., Northbrook, IL, USA; [13]Pfizer Inc., New York, NY, USA

Nonauthor presenter: Charlene Whittlesey[12]

Objective

- To develop a consensus on best practices for early identification and management of enfortumab vedotin (EV)–associated peripheral neuropathy (PN), including how to counsel patients who are initiating EV, and their caregivers, on short- and long-term PN monitoring

Conclusions

- This multidisciplinary panel, which included a patient representative, provided a diverse, real-world perspective for developing the first expert consensus on the clinical decision-making and management of EV-related PN in patients with urothelial carcinoma (UC). Panelists urge the use of shared decision making
- These recommendations reflect best practices from existing guidelines in managing chemotherapy-induced neuropathic pain, trial data, product information, and clinical experience in managing EV
- The recommendations for PN assessments throughout the treatment cycle are intended to close the gap between the clinical grading of PN and the patient's subjective experience of its severity and functional impact[4]
- These recommendations can be used to improve the management of patients with UC receiving EV ± pembrolizumab and provide guidance on the early identification and diagnosis of EV-associated PN, EV dose modifications, interventions and referrals, and patient and caregiver education

References

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Conflicts of Interest

AD received grants or contracts to their institution from Acrivon, Adcentrx, AstraZeneca, Daiichi Sankyo, Lilly, Merck, Pfizer, and Roche; received consulting fees from AstraZeneca; received support for attending meetings/travel from AstraZeneca, Lilly, and Loxo; participated on a data safety monitoring or advisory board for AstraZeneca, Daiichi Sankyo, Exelixis, Janssen, Lilly, and Pfizer; and serves in a leadership or fiduciary role with the American Association for Cancer Research, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network. **CW** is an employee of Astellas.

Acknowledgments

This study was funded by Astellas Pharma Inc. and Pfizer. Medical writing support was provided by Pedro de Campos Silva, PhD, on behalf of Lumanity Scientific Inc., and was funded by Astellas Pharma Inc. and Pfizer.

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For more information, please contact: Alexandra Drakaki, adrakaki@mednet.ucla.edu

Presented at the Florida Society of Clinical Oncology Spring Congress; April 10–11, 2026; Orlando, FL, USA. Previously presented at the American Society of Clinical Oncology Genitourinary Cancers (ASCO GU) Symposium; February 26–28, 2026; San Francisco, CA, USA, and Online.

Background

- EV + pembrolizumab is approved in the first-line and perioperative settings for patients with locally advanced or metastatic urothelial carcinoma (la/mUC) and cisplatin-ineligible muscle-invasive bladder cancer, respectively[1]
  - In both indications, patients treated with EV + pembrolizumab experienced significant improvements in event-free survival, progression-free survival, and overall survival[5,6]
- PN is a potentially dose-limiting adverse event associated with EV ± pembrolizumab[6,7–10]
- Early identification and management of PN is a critical part of optimizing patient outcomes[9]
- Given the clinical relevance of PN, there is a desire to provide further information on the recognition and management of EV-associated PN in UC

Methods

- This was a RAND/University of California Los Angeles–modified Delphi panel composed of 5 medical oncologists, 3 neurologists, 1 pharmacist, 1 physiatrist, 1 nurse practitioner, and 1 patient advocate from the United States with experience in managing patients with la/mUC who are being treated with EV ± pembrolizumab
- The panel received a summary of the targeted literature review, followed by a live discussion in between 2 electronic surveys that contained different PN management strategies and scenarios (**Figure 1**)
  - Electronic survey questions were either qualitative or quantitative and rated on a scale from 1 to 9, with a higher number reflecting greater appropriateness (benefits increasingly outweighing the risks) of the scenario or management strategy. Ratings were analyzed and classified into agreement or disagreement categories based on the median and range of each score provided (**Table 1**)

Figure 1: Study Design

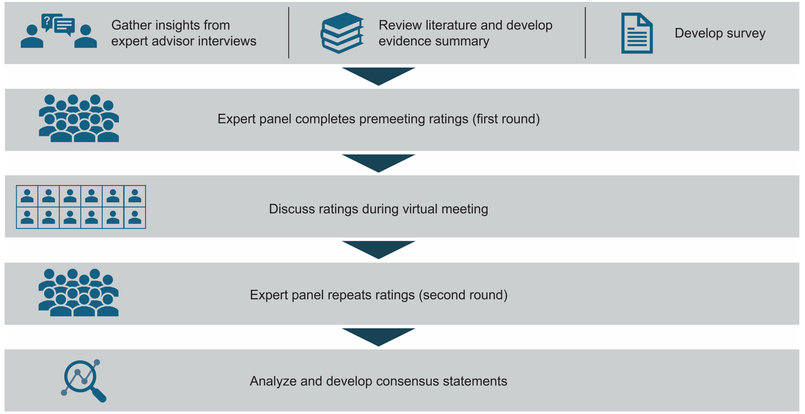


Table 1: Analysis of Rating Scores for the RAND/UCLA Modified Delphi Panel

Agreement	Median score of ≥7 to 9, without disagreement	Experts agree that the approach is **appropriate**
	Median score of ≥4 to <7, or any median with disagreement	Experts agree that the approach **may or may not be appropriate**
	Median score of 1 to <4, without disagreement	Experts agree that the approach is **inappropriate**
Disagreement	≥2 scores of 1–3 and ≥2 scores of 7–9 for the same rating	**No conclusions** can be made

UCLA, University of California Los Angeles.

Results

Targeted Literature Review

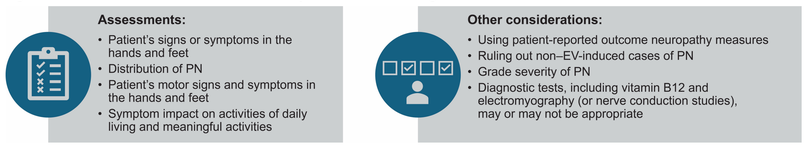
- The targeted literature review revealed no consensus recommendations for EV-associated PN

Delphi Results – Consensus Statements

Early Identification and Diagnosis

- At treatment initiation after every cycle and at the end of treatment, several assessments and other considerations were rated as appropriate for the early identification and diagnosis of PN (**Figure 2**)

Figure 2: Consensus Recommendations for the Early Identification and Diagnosis of EV-Associated PN

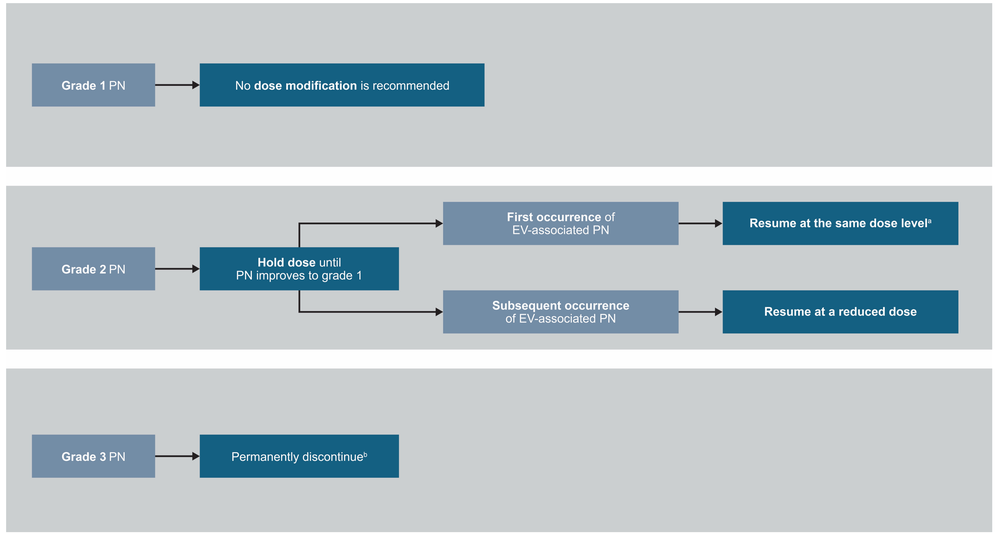


EV, enfortumab vedotin; PN, peripheral neuropathy.

EV Dose Modifications During First and Subsequent Occurrences of EV-Associated PN

- During the occurrence of EV-associated PN, different EV dose modifications were recommended depending on the severity of PN (**Figure 3**)

Figure 3: Consensus Recommendations for EV Modifications During an Occurrence of EV-Associated PN



In the final survey, different clinical characteristics such as PN-related comorbidities, response to EV, ECOG PS score, and PN severity were considered within each hypothetical scenario as well as in potential interventions. In patients with pre-existing neuropathy, clinicians should proactively identify and manage relevant comorbidities and risk factors (e.g., optimize glycemic control in patients with diabetes). PN-relevant comorbidities included uncontrolled diabetes, peripheral vascular disease, or resolved drug-induced PN.
[a]Consider restarting at a lower dose if PN has rapidly worsened or the patient is responding.
[b]For patients whose PN improves to ≤1, resuming EV at a lower dose may be appropriate. Key considerations when assessing the risk/benefit of restarting treatment may include performance status, goals of care, tumor burden, and management of PN-related comorbidities.
ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; PN, peripheral neuropathy.

Other Interventions and Referrals

- Other interventions and referrals were generally recommended depending on PN severity and patient characteristics (**Table 2**)

Table 2: Consensus Recommendations for Other Interventions and Referrals During EV-Associated PN

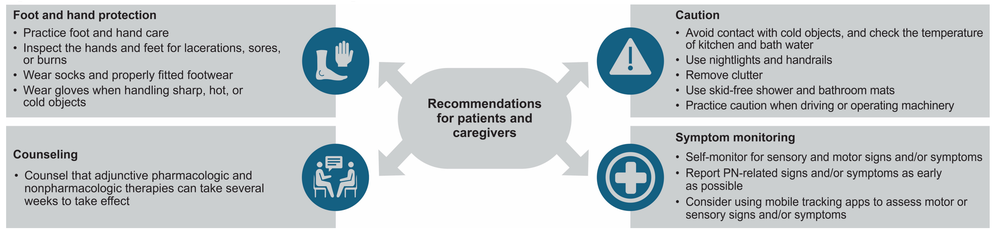
Intervention/referral	Grade 1 PN	Grade 2 PN	Grade 3 PN
Pharmacologic therapies[a]	Consider only if the patient has positive symptoms,[b] an ECOG PS score of 2, and active pre-existing PN	Positive symptoms: recommend[b] Negative symptoms: do not recommend[b,c]	Positive symptoms: recommend[b] Negative symptoms: consider[b]
Nonpharmacologic therapies[a]	Recommended	Recommended	Recommended
Referral to neurology[d]	Consider in all cases, except for patients with an ECOG PS score of 1, no active pre-existing PN, and no PN-relevant comorbidities present	Consider if the patient has no active pre-existing PN and no PN-relevant comorbidities; recommended for all other cases	Recommended
Referral to PT/OT/physiatry	Consider if the patient has no active pre-existing PN, no PN-relevant comorbidities, and positive symptoms[b]	Consider if the patient has no active pre-existing PN and no PN-relevant comorbidities; recommended for all other cases	Recommended

[a]Pharmacologic and nonpharmacologic adjunctive therapies are based on the 2020 American Society of Clinical Oncology guidelines on the prevention and management of chemotherapy-induced PN.[2]
[b]Positive symptoms include abnormal sensations such as pain, tingling, burning, and itching. Negative symptoms include abnormal sensations such as numbness, muscle weakness, and loss of balance.
[c]Consider for patients with active pre-existing PN (with or without PN-relevant comorbidities present).
[d]Patients should be referred to neurology, particularly if presentation is atypical (eg, rapid onset, proximal weakness, cranial nerve involvement), to evaluate for immune-related neurologic adverse events.
ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; OT, occupational therapy; PN, peripheral neuropathy; PT, physical therapy.

Recommendations for Patient and Caregiver Education

- Several patient and caregiver actions were considered appropriate at treatment initiation, 3 months after treatment initiation, and following the appearance of PN symptoms (**Figure 4**)

Figure 4: Consensus Recommendations for Patient and Caregiver Education



PN, peripheral neuropathy.