The Voice of Urology in Canada

Canadian Urological Association

The Voice of Urologic Oncology in Canada

Enfortumab Vedotin (EV) and Pembrolizumab (Pembro) Combination Treatment for Patients with Urological Cancers – **Adverse Events (AEs)**

Management Tool Kit

Contents

Enfortumab Vedotin (EV) and Pembrolizumab (Pembro) Combination Treatment for Patients with Urological Cancers – **Adverse Events (AEs)**

Management Tool Kit

Background[1-14]

Enfortumab vedotin (EV) and **Pembrolizumab (Pembro)** have individually demonstrated significant improvements in overall survival (OS) in patients with advanced urological cancers.

EV is an antibody-drug conjugate (ADC) that targets the cellular receptor, Nectin-4, found on the surface of most urothelial cancer cells, and uses a microtubule-disrupting agent to induce cell cycle arrest and apoptosis. **Pembro is an immune checkpoint inhibitor (ICI)** that prevents the deactivation of the Programmed cell death protein 1 (PD-1) receptor. The combination of EV + Pembro for the first-line treatment of advanced urothelial carcinoma has shown significant improvements in both OS and progression-free survival (PFS), compared to platinum-based chemotherapy (EV-302 Phase 3 clinical trial).

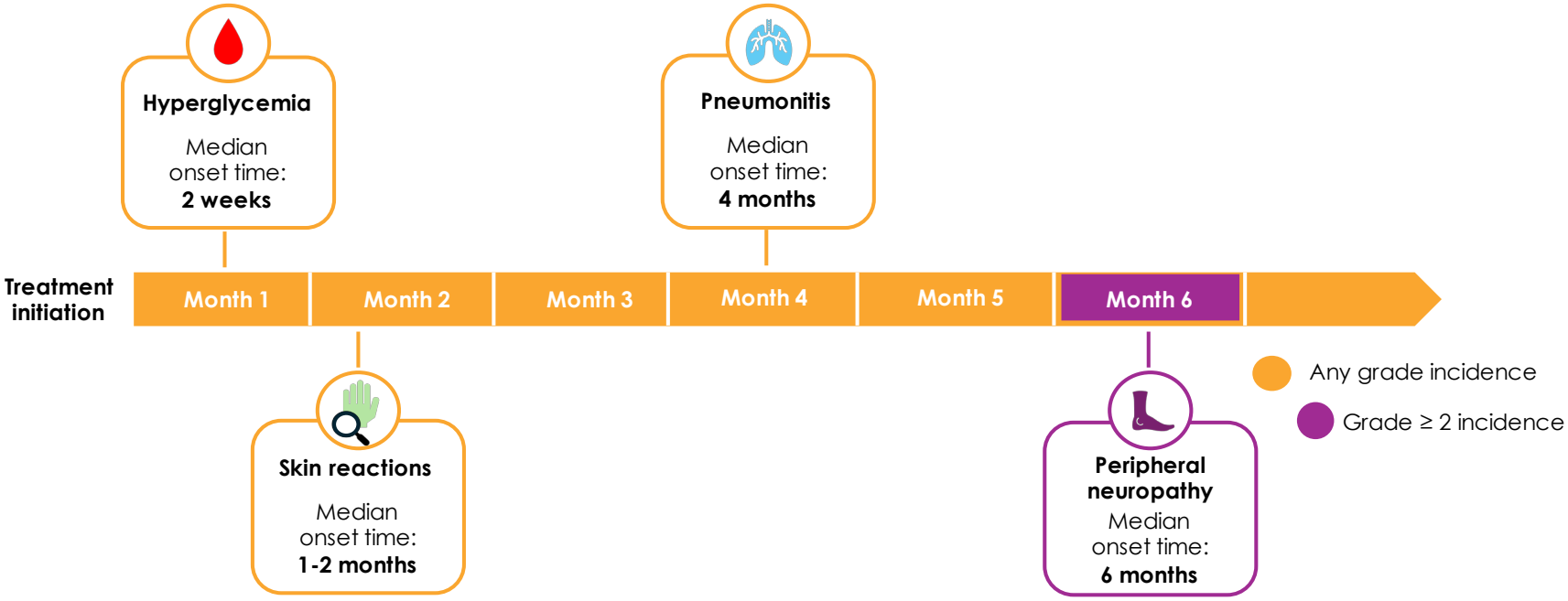
Both EV and Pembro, as monotherapies, are associated with AEs typical of their respective therapeutic classes. Clinically relevant AEs associated with the use of either EV, Pembro, or both, include:

When EV and Pembro are used together, it can be challenging to identify which drug is responsible for a specific AE and to determine the most effective management approach. However, the timing and presentation of certain AEs, such as peripheral neuropathy, may help discern the causative agent. **This tool kit aims to provide concise guidance for management of AEs arising from EV and Pembro combination therapy.**

Tool card development lead: Aly-Khan Lalani, MD, FRCPC.

Tool card review committee: Nimira Alimohamed, MD, FRCPC; Joël Claveau, MD, FRCPC; Sébastien S. Dufresne, PT PhD; Warren Mason, MD, FRCPC; Maxwell Sauder, MD, FRCPC; Minna Woo, MD, FRCPC, PhD.

Figure 1. *Clinically relevant AEs associated with EV+Pembro treatment and their median onset time.*



Please note that these AEs can present at any time, the median onset is depicted here.
AE, adverse event; EV, enfortumab vedotin; Pembro, pembrolizumab.

General guidelines for the management of EV+Pembro associated AEs[14-18]

Most AEs can be effectively managed through early detection and timely medical intervention, often requiring dose modifications or interruptions. Close monitoring of patients, along with active collaboration between the patient, caregivers, and a multidisciplinary team of specialists, is essential for the early identification of AEs.

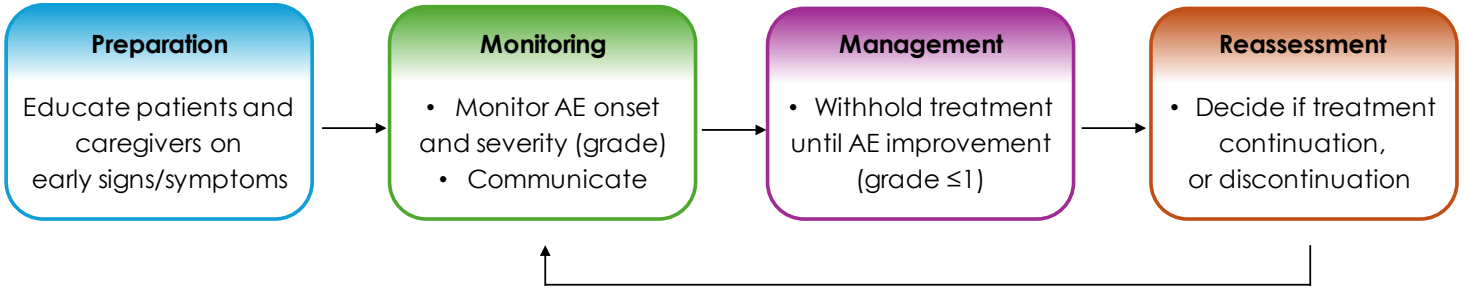
In severe cases, when patients experience rapid onset of AEs (grade ≥3), **both therapies should be withheld** until the patient's symptoms improve and AEs reduce to grade ≤1; therapies should be permanently discontinued or withheld until grade ≤1 (**Figure 2**).

AEs can occur at any point during treatment.

EV: Those associated with EV typically emerge within the first few weeks after initiation, but can also develop months later. Common AEs related to EV monotherapy are skin reactions, gastrointestinal and neurologic issues, as well as ophthalmic reactions.

Pembro: AEs related to Pembro are primarily immune-related (irAEs), including skin reactions, gastrointestinal disturbances, lung issues, and AEs affecting the endocrine or musculoskeletal systems. Cardiovascular, hematologic, renal, neurologic, and ophthalmologic irAEs are less common. irAEs can occur early upon treatment initiation, but their onset is usually delayed (months after treatment start). Dose modifications of Pembro are not recommended; instead, dose withholding is advised in the event of irAEs.

Figure 2. *General AE management algorithm recommended for EV+Pembro treatment.*



AE, adverse event; EV, enfortumab vedotin; Pembro, pembrolizumab.

Clinically relevant AEs associated EV+Pembro treatment

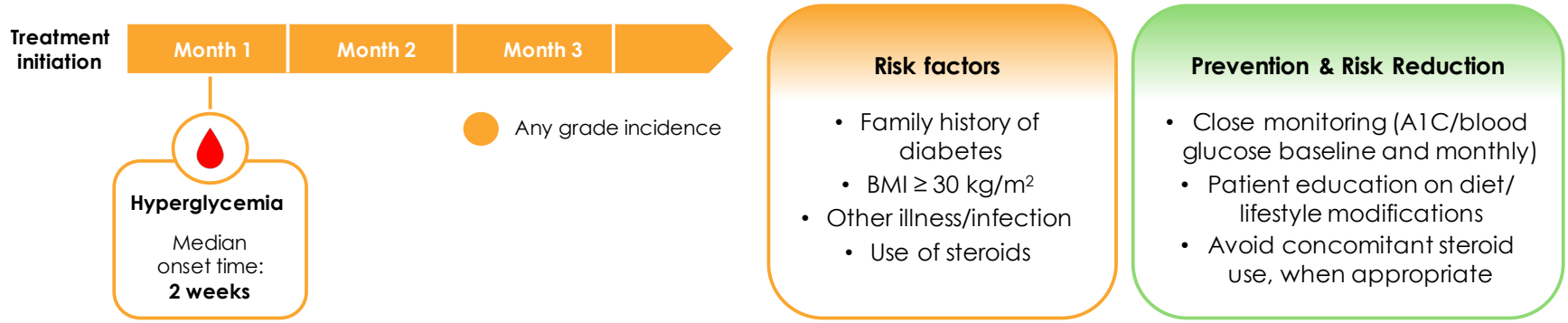
Hyperglycemia[14, 15, 18-20]

Hyperglycemia can occur during treatment with the EV+Pembro combination or as a result of the individual therapies; though it is rarely associated with Pembro monotherapy (0.2% of patients) compared to EV monotherapy (17%). Although rare, if hyperglycemia is expected to be **related to pembrolizumab, consult an endocrinologist.** With EV+Pembro, median time to onset of hyperglycemia was 2 weeks after initiating treatment (**Figure 1, Figure 3**).

Hyperglycemia risk is higher in patients with BMI ≥ 30 kg/m^2, family history of diabetes, infections or steroid use. Prevention strategies for hyperglycemia include close patient monitoring, patient education on diet/lifestyle adjustments, and avoiding concomitant steroid use, when possible. Additionally, at baseline, c-peptide, A1C and non-fasting blood glucose (i.e., random blood glucose) should be measured, followed by monthly A1C and glucose blood work thereafter (**Figure 3**). Endocrinologists suggest ordering A1C tests in addition to blood glucose assessments, as they help inform management decisions by providing a comprehensive clinical understanding of patients' blood glucose control over time.

Recommendations for the monitoring and management of treatment-related hyperglycemia can be found in **Figure 4**.

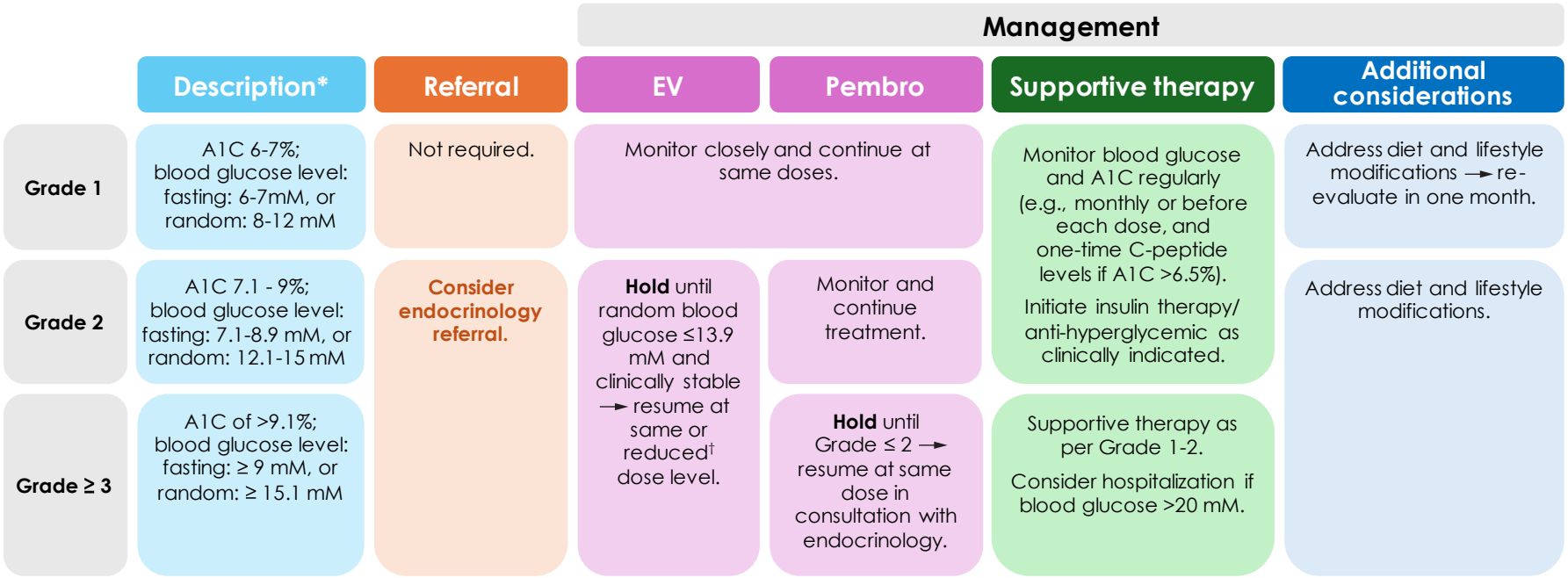
Figure 3. *Median onset time of any grade hyperglycemia upon EV+Pembro treatment, described risk factors for hyperglycemia and prevention recommendations.*



Ordering A1C tests in addition to blood glucose assessments are recommended as they can inform management decisions by offering a comprehensive clinical understanding of patients' blood glucose control over time.

BMI, body mass index; EV, enfortumab vedotin; Pembro, pembrolizumab.

Figure 4. *Monitoring and management of treatment-related hyperglycemia*



*Quantitative values according to expert clinical judgement, informed by Diabetes Canada Clinical Practice Guidelines.
†Recommended dose reduction schedule for EV can be found in **Table 2** (p. 15).
EV, enfortumab vedotin; Pembro, pembrolizumab.

Skin reactions[12, 14, 15, 21-25]

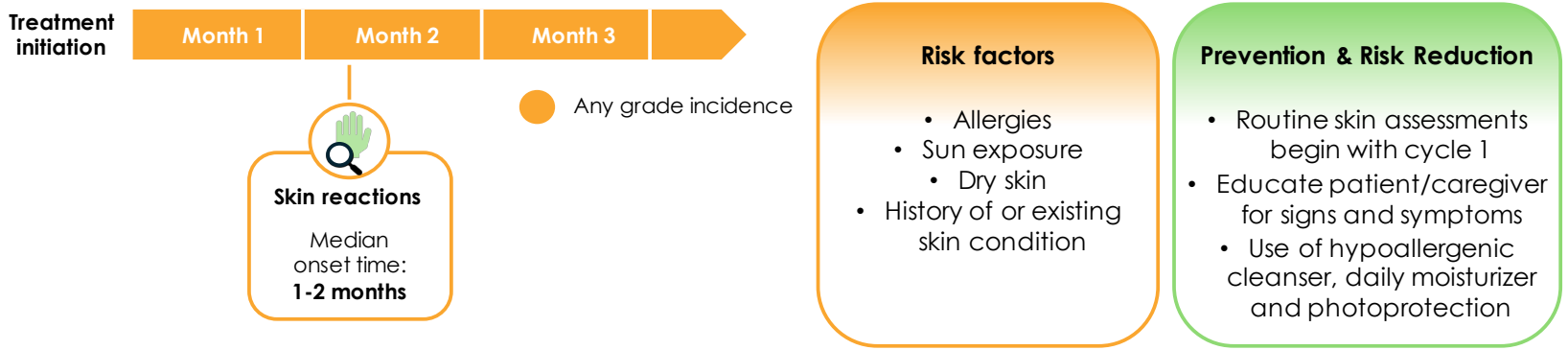
All grade skin reactions occur in the majority of patients (70%) treated with EV+Pembro. The median time of onset for severe skin reactions (grade 3-4) is 1.7 months (**Figure 1, Figure 5**). Notably, events can occur as early as the first treatment cycle. Most common skin reactions arising from EV+Pembro treatment are maculopapular rash, pruritus, dry skin, and SDRIFE (symmetrical drug-related intertriginous and flexural exanthema). SDRIFE and other intertriginous reactions due to EV typically occur early in the treatment course (i.e., within first 2 months). The most common immunotherapy cutaneous adverse events include: pruritus without primary dermatologic findings, eczematous, psoriasiform, lichenoid, exanthematous and bullous eruptions, often after 2 months.

Cases of Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) have occurred with EV and Pembro, predominantly during the first cycle of treatment, but may occur later. SJS/TEN can be fatal; early identification and close monitoring are crucial. Specifically, SJS/TEN or other significant cutaneous adverse reactions (SCARs) should be suspected if patients present with a rash as well as any of the following signs/symptoms: fever, blisters or skin detachment, skin pain, mucous membrane involvement and significant change in laboratory abnormalities.

Skin reactions or exacerbations can especially occur in people with a history of, or pre-existing, skin conditions, including immune-related ones. With pre-emptive counselling on a basic dermocosmetic routine and education for signs/symptoms, skin reactions can be delayed and reduced in incidence and severity. Specifically, counselling on cleansing with hypoallergenic pH balanced cleansers, moisturizing daily (cream or balm), and use of photoprotection can help (**Figure 5**). It is important to educate patients and caregivers on dermatological risks and symptoms and advise them to report new or changing skin reactions promptly.

Recommendations for the monitoring and management of treatment-related skin reactions can be found in **Figure 6**.

Figure 5. *Median onset time of any grade skin reactions upon EV+Pembro treatment, described risk factors for skin AEs and recommendations for their prevention*



AE, adverse event; EV, enfortumab vedotin; Pembro, pembrolizumab.

Figure 6. *Monitoring and management of treatment-related skin reactions*

	Description	Referral	Management			
			EV	Pembro	Supportive therapy	Corticosteroids
Grade 1	Exanthematous rash ≤10% BSA without additional signs/symptoms*	Not required.	Monitor and continue at same doses.		Supportive care as clinically indicated (e.g., emollients ± antihistamines, antibiotics, antipruritic) → reassess frequently.	Mid-potency topical steroids at dose level appropriate for management (e.g., desonide cream BID in large amounts)
Grade 2	Between Grade 1 and 3 (e.g., exanthematous rash >10% without additional signs/symptoms)*	**Consider dermatology referral.** Consider biopsy.	Manage per Grade 1; requires frequent reassessment. if worsening, withhold both agents until Grade ≤1.			
Grade 3	Exanthematous rash >10% BSA with ≥1 additional sign or symptom* OR erythroderma (>90% BSA) OR marked rapidly evolving, painful large skinfold involvement.	**Consider dermatology referral.** **Biopsy of a few sites + IF.**	**Immediately hold** until Grade ≤ 1 → resume at same or reduced dose† level.	**Hold** until Grade ≤ 1 → consider resuming in consultation with dermatology.	Consider hospitalization. Supportive care per Grade 1-2.	Mid-potency topical steroids (e.g., betamethasone valerate 0.1% cream BID) ± systemic corticosteroids (0.5-1 mg/kg QD), as appropriate.
Suspected SJS/TEN	Malaise, fever ≥ 38°C, mucosal involvement (ocular, oral, genital) or dermatodynia.	**Urgent dermatology consult ± ER assessment.** **Biopsy of a few sites + IF.**	**Immediately hold** both agents. Manage per Grade 2-4 depending on diagnosis.		Hospitalization with specialized care (burn unit or ICU).	Systemic corticosteroids (1-2 mg/kg QD) ± adjuvant treatment for SJS/TEN (e.g., cyclosporine, etanercept, plasmapheresis)
Grade 4 or recurrent Grade 3	Grade 3 description; confirmed SJS/TEN or severe skin reaction; any signs of desquamation.		**Permanently discontinue** both therapies.			

***Additional signs and symptoms, including RED FLAGS:**

- Skin fold involvement
- Severe pruritus, burning, or skin pain
- Blisters, or detachment
- Mucosal involvement or skin erosions
- Fever ≥38°C or general condition decline
- Unexplained biological abnormalities (blood count, liver, kidney, CRP; ≥1 Grade increase)

Patients exhibiting RED FLAGS need to go to the ER

This figure was developed based on the literature[12, 14, 15, 21-25], and clinical expert opinion (dermatologists, medical oncologists).

†Recommended dose reduction schedule for EV can be found in **Table 2** (p. 15).

BID, twice daily; BSA, body surface area; CRP, C-reactive protein; ER, emergency room; EV, enfortumab vedotin; ICU, intensive care unit; IF, immunofluorescence; QD, once daily; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; Pembro, pembrolizumab; ULN, upper limit normal (per baseline value).

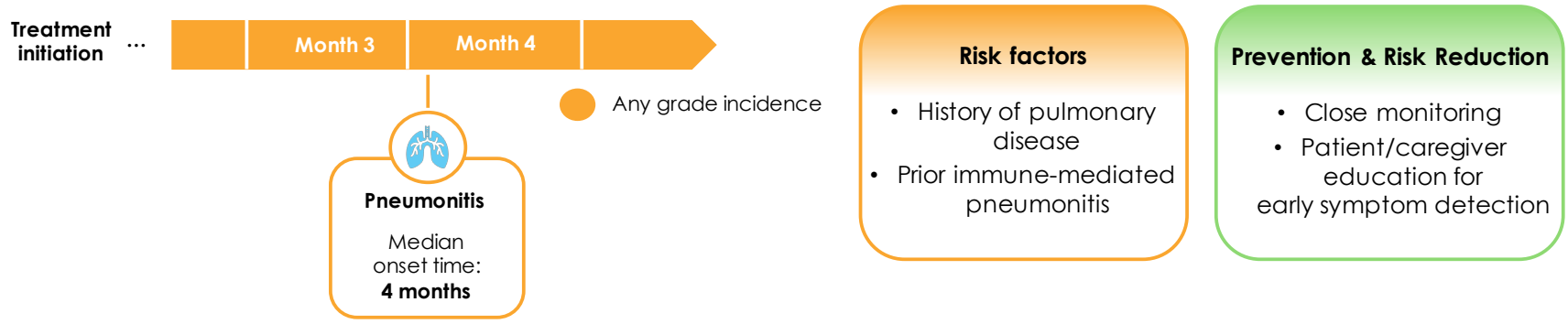
Pneumonitis[14, 15, 18, 26]

Pneumonitis (grade ≥3) arises in approximately <1% of patients treated with EV or Pembro monotherapies, and more frequently in patients treated with EV+Pembro combination therapy (10% grade ≥3). The median time to onset of any grade pneumonitis upon EV+Pembro treatment initiation was 4 months (**Figure 1, Figure 7**).

Risk factors for pneumonitis include a history of prior pneumonitis and underlying pulmonary diseases. Preventative strategies include close patient monitoring and early symptom recognition to mitigate higher grade disease, as well as patient education on symptom identification (**Figure 7**).

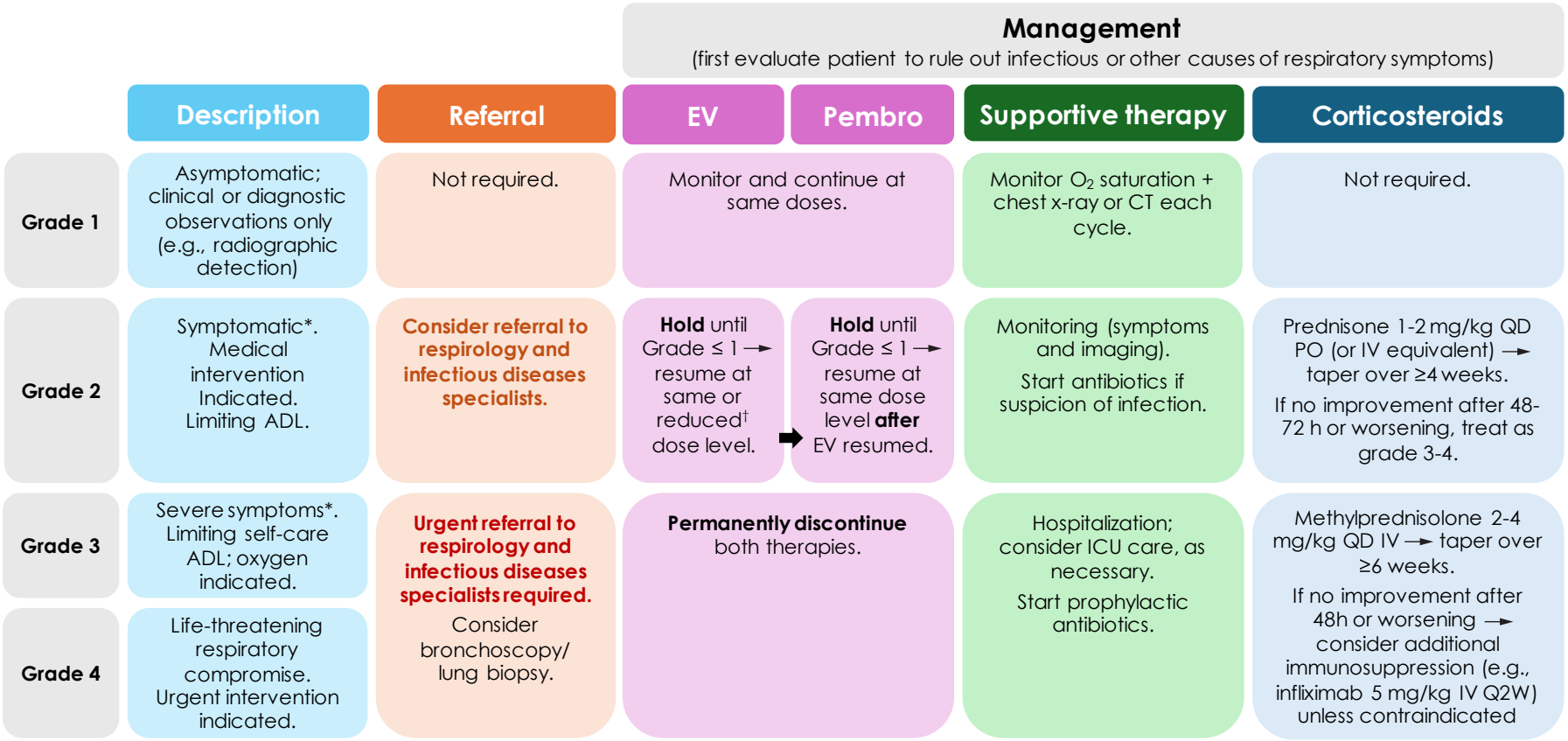
Recommendations for the monitoring and management of treatment-related pneumonitis can be found in **Figure 8**.

Figure 7. *Median onset time of any grade pneumonitis upon EV+Pembro treatment, described risk factors for pneumonitis and prevention recommendations.*



AE, adverse event; EV, enfortumab vedotin; Pembro, pembrolizumab.

Figure 8. *Monitoring and management of treatment-related pneumonitis*



*** Symptomatic pneumonitis:**
- Hypoxia, cough, dyspnea
- Radiological evidence of interstitial infiltrates

†Recommended dose reduction schedule for EV can be found in **Table 2** (p. 15).

ADL, activities of daily living; CT, computerized tomography; EV, enfortumab vedotin; h, hour; ICU, intensive care unit; IV, intravenous; Pembro, pembrolizumab; PO, orally; QD, once daily; Q2W, every two weeks.

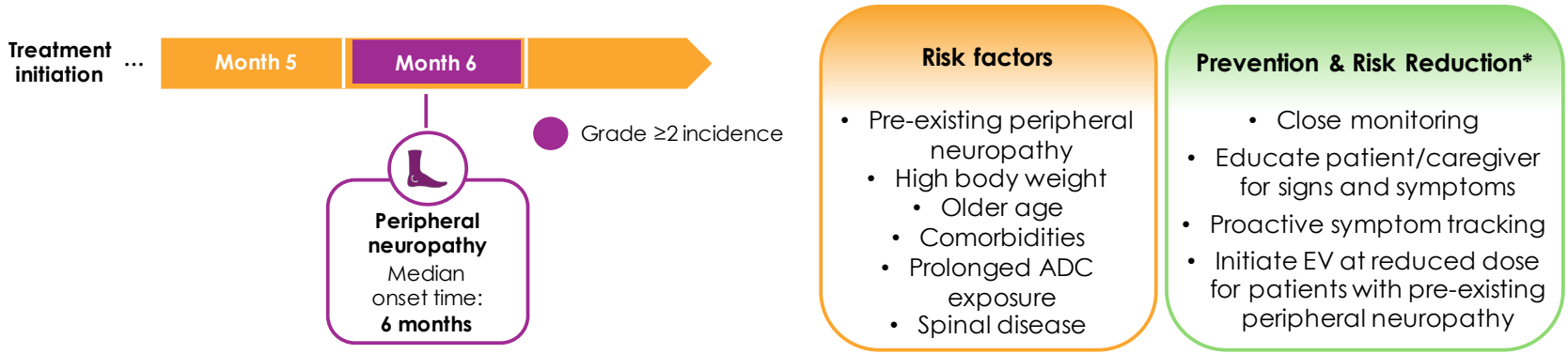
Peripheral neuropathy[5, 14, 15, 18, 27-31]

Peripheral neuropathy is the second most common AE arising from EV+Pembro treatment, occurring in 67% of patients (grade 3 in 7% of patients) and it was the most common AE leading to EV discontinuation. Peripheral neuropathy is an AE typically associated with ADCs; such neuropathies are dose-dependent, develop gradually, and worsen with continued treatment. The median time to onset is 6 months for grade ≥2 peripheral neuropathy (**Figure 1, Figure 9**); early signs may present sooner. Timely management is crucial to maximize recovery potential and prevent further deterioration. Immune-related peripheral neuropathies (i.e., attributable to Pembro) are rare, but often severe in nature, progress rapidly, and generally require urgent medical management.

Peripheral neuropathies, particularly those grade ≥2, are associated with various risk factors, such as **pre-existing peripheral neuropathies and high body weight. Cumulative drug exposure and prolonged treatment duration also increased risk of development.** Strategies for the prevention of peripheral neuropathies involve close patient monitoring and patient education on signs and symptoms, as timely symptom recognition to prevent higher grade AEs (**Figure 9**). **For patients with pre-existing peripheral neuropathies, consider initiating therapy with a reduced dose to mitigate neurotoxicity risk.**

Clinical spectrum and symptom progression of peripheral neuropathy and recommendations for the monitoring and management of treatment-related peripheral neuropathy can be found in **Table 1** and **Figure 10**, respectively.

Figure 9. *Median onset time of grade ≥2 peripheral neuropathy upon EV+Pembro treatment, described risk factors for peripheral neuropathy and prevention recommendations.*



*Due to the cumulative effect of EV, patients who develop symptoms early in treatment may be at a higher risk for severe and long-lasting neuropathy.
ADC, antibody-drug conjugate; EV, enfortumab vedotin; Pembro, pembrolizumab.

Table 1. *Clinical spectrum and symptom progression in peripheral neuropathy*

Type	Early Stage – potential symptoms	Intermediate Stage	Advanced Stage
Sensory	• Tingling, burning or stabbing sensation in hands/feet • Proprioception disturbances • Mild numbness or pain	• Loss of sensation • Worsening/spreading numbness • Worsening pain • Impaired balance/coordination	• Complete loss of pain/temperature sensation • Significant proprioception loss (e.g., gait and balance issues, falls) • Loss of reflexes
Motor	• Mild muscle weakness in hands/feet • Difficulty with fine motor tasks • Occasional muscle cramps or twitching	• Progressive muscle weakness in legs/arms • Foot drop • Loss of mobility; muscle atrophy in hands/feet	• Severe muscle atrophy • Paralysis in affected muscles • Severe loss of mobility; joint stiffness
Autonomic	• Occasional dizziness (orthostatic hypotension) • Mild digestive issues • Change in sweating (reduced or excessive)	• Frequent dizziness, near-fainting episodes • Chronic constipation or gastroparesis • Urinary issues • Erectile dysfunction in men	• Severe blood pressure fluctuations, fainting • Malnutrition • Bladder dysfunction • Anhidrosis

This table was developed based on the literature[5, 14, 15, 18, 27-31], and clinical expert opinion (neurologists, medical oncologists).

Figure 10. *Monitoring and management of treatment-related peripheral neuropathy*

			Management			
	Description	**Referral**	**EV**	**Pembro**	**Supportive therapy***	**Immune-therapy**
Early stage (~Grade 1)	Early-stage symptoms per Table 1	Neurologic consult required for early motor or autonomic symptoms.	Monitor; consider proactive dose reduction† or hold.	Monitor; consider holding until return to baseline.	**1L:** Symptom management (e.g., duloxetine, TCAs, gabapentin†); physical/occupational therapy. **2L:** opioid analgesics; **3L+:** stronger opioids, non-gabapentinoid AEDs, or cannabinoids.	Not required.
Intermediate stage (~Grade 2)	Intermediate-stage symptoms per Table 1; limit IADL.	**Consider neurology referral.** Consider MRI, NCS, EMG, lumbar puncture. Workup for immune-mediated etiology. **OR** **Urgent neurology referral** if MG, GBS, encephalitis is suspected, or any other red flag features are present.	**Hold** until return to baseline → resume at reduced† dose level.	**Hold** until return to baseline → may resume after analysis of benefit/risks.		If irAE, rapid intervention with immunosuppressive therapies, including corticosteroids or other agents (e.g., infliximab, mycophenolate mofetil) until return to baseline. Consider IVIG, plasmapheresis, or supportive medications, as clinically indicated.
Advanced/ severe stage (~Grade 3-4)	Advanced-stage symptoms per Table 1; **urgent intervention indicated**. **RED FLAG features:** rapid symptom progression (over days/weeks), proximal muscle weakness, loss of reflexes w/o significant sensory impairment; cranial nerve deficits.		**Permanently discontinue if not immune-related.** **If irAE**, continue at same or reduced† dose level in consult with neurology.	**Permanently discontinue if not immune-related.** **If irAE, hold** until return to baseline → may resume after analysis of benefit/risks.	Supportive therapy per early/intermediate or other supportive medications, as clinically indicated.	

This figure was developed based on the literature[5, 14, 15, 18, 27-31], and clinical expert opinion (neurologists, medical oncologists).
Categorization and descriptions for early, intermediate and advance/severe-stage peripheral neuropathy were developed to address the nature of neuropathy itself (i.e., sensory, motor, or autonomic in origin) which is crucial for timely identification and optimizing patient care. Additionally, this can help to differentiate between typical drug-induced neuropathy and presentations that may suggest alternative or more serious etiologies requiring urgent neurologist intervention. Severity grades are in brackets to help address typical peripheral neuropathy grading classifications.

*Only positive symptoms (e.g., pain) can be managed by pharmacological treatments, and generally require >6 weeks for significant therapeutic benefit. Negative symptoms (e.g., loss of sensation, weakness, motor symptoms) require rehabilitation; early rehabilitation is important to maximize recovery potential.
†Recommended dose reduction schedule for EV can be found in **Table 2** (p. 15).
‡Pregabalin has not shown effectiveness for chemotherapy-induced peripheral neuropathy symptoms.
1L, first line; 2L, second line; 3L, third line; AED, antiepileptic drug; EMG, electromyogram; EV, enfortumab vedotin; IADL, instrumental activities of daily living; irAE, immune-related adverse event; IVIG, intravenous immunoglobulin; MG, myasthenia gravis; MRI, magnetic resonance imaging; NCS, nerve conduction survey; Pembro, pembrolizumab; TCA, tricyclic antidepressants.

Appendix[15, 18]

Dose reductions of EV may be recommended for the management of treatment-related AEs depending on the severity (**Figure 4**, **Figure 6**, **Figure 8**, **Figure 10**). The recommended dose reduction schedule for EV is shown in **Table 2**. Please note that dose reductions are not recommended for Pembro.

Table 2. *Enfortumab vedotin dose reduction schedule*

Dose Level	Dosage
Starting dose	1.25 mg/kg up to 125 mg
First dose reduction	1.0 mg/kg up to 100 mg
Second dose reduction	0.75 mg/kg up to 75 mg
Third dose reduction	0.5 mg/kg up to 50 mg

References

1. Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee JL, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med.* 2021;384:1125–35. DOI: 10.1056/NEJMoa2035807.

2. Yu EY, Petrylak DP, O'Donnell PH, Lee JL, van der Heijden MS, Loriot Y, et al. Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV−201): a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2021;22:872–82. DOI: 10.1016/S1470-2045(21)00094-2.

3. Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm study. *Lancet Oncol.* 2017;18:1483–92. DOI: 10.1016/S1470-2045(17)30616-2.

4. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med.* 2017;376:1015–26. DOI: 10.1056/NEJMoa1613683.

5. Hoimes CJ, Flaig TW, Milowsky MI, Friedlander TW, Bilen MA, Gupta S, et al. Enfortumab vedotin plus pembrolizumab in previously untreated advanced urothelial cancer. *J Clin Oncol.* 2023;41:22–31. DOI: 10.1200/JCO.22.01643.

6. O'Donnell PH, Milowsky MI, Petrylak DP, Hoimes CJ, Flaig TW, Mar N, et al. Enfortumab vedotin with or without pembrolizumab in cisplatin-ineligible patients with previously untreated locally advanced or metastatic urothelial cancer. *J Clin Oncol.* 2023;41:4107–17. DOI: 10.1200/JCO.22.02887.

7. Powles T, Perez-Valderrama B, Gupta S, Bedke J, Kikuchi E, Hoffman-Censits J, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med.* 2024;390:875–88. DOI: 10.1056/NEJMoa2312117.

8. National Comprehensive Cancer Network. Management of immunotherapy-related toxicities. NCCN Clinical Practice Guidelines in Oncology. 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf.

9. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO clinical practice guideline. *J Clin Oncol.* 2018;36:1714–68. DOI: 10.1200/JOP.18.00005.

10. Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017;28:iv119–iv42. DOI: 10.1093/annonc/mdx225.

11. Brahmer JR, Abu-Sbeih H, Ascierto PA, Brufsky J, Cappelli LC, Cortazar FB, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J Immunother Cancer.* 2021;9:e002435. DOI: 10.1136/jitc-2021-002435.

12. Lacouture ME, Patel AB, Rosenberg JE, O'Donnell PH. Management of dermatologic events associated with the Nectin-4-directed antibody-drug conjugate enfortumab vedotin. *Oncologist.* 2022;27:e223–e32. DOI: 10.1093/oncolo/oyac001.

13. Pace A, Brower B, Conway D, Leis D. Enfortumab vedotin: Nursing perspectives on the management of adverse events in patients with locally advanced or metastatic urothelial carcinoma. *Clin J Oncol Nurs.* 2021;25:E1–9. DOI: 10.1188/21.CJON.E1-E9.

14. Brower B, McCoy A, Ahmad H, Eitman C, Bowman A, Rembisz J, Milowsky MI. Managing potential adverse events during treatment with enfortumab vedotin + pembrolizumab in patients with advanced urothelial cancer. *Front Oncol.* 2024;14:1326715. DOI: 10.3389/fonc.2024.1326715.

15. Seagen, Astellas Pharma US Inc. PADCEV (enfortumab vedotin-ejfv) for injection. 2023. Available at: https://astellas.us/docs/PADCEV_label.pdf.

16. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *J Clin Oncol.* 2018; 36:1714–68. DOI: 10.1200/JOP.18.00005.

17. Wu Z, Chen Q, Qu L, Li M, Wang L, Mir MC, et al. Adverse events of immune checkpoint inhibitors therapy for urologic cancer patients in clinical trials: a collaborative systematic review and meta-analysis. *Eur Urol.* 2022;81:414–25. DOI: 10.1016/j.eururo.2022.01.028.

18. Merck & Co. KEYTRUDA (pembrolizumab) injection. 2024. Available at: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.

19. Kotwal A, Haddox C, Block M, Kudva YC. Immune checkpoint inhibitors: an emerging cause of insulin-dependent diabetes. *BMJ Open Diabetes Res Care.* 2019;7:e000591. DOI: 10.1136/bmjdrc-2018-000591.

20. Ekoe JM, Goldenberg R, Katz P. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Screening for Diabetes in Adults. *Can J Diabetes.* 2018;42(Suppl 1):S16–9.

21. Ingen-Housz-Oro S, Elshot YS, Segura S, Marchand A, Pouessel D, Kluger N, et al. Skin toxicity of enfortumab vedotin: Proposal of a specific management algorithm. *J Eur Acad Dermatol Venereol.* 2024;38:e99–e101. DOI: 10.1111/jdv.19454.

22. Sauder MB, Claveau J, Butler M, Andriessen A, Hijal T, Lynde CW. CaSMO Management of Cutaneous Toxicities Associated with Immune Checkpoint Inhibitors: A Practical Primer. *Skin Therapy Lett.* 2022;Suppl.

23. Belum VR, Benhuri B, Postow MA, Hellmann MD, Lesokhin AM, Segal NH, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer.* 2016;60:12–25. DOI: 10.1016/j.ejca.2016.02.010.

24. Halle BR, et al. Immune checkpoint inhibitors in patients with pre-existing psoriasis: safety and efficacy. *J Immunother Cancer.* 2021;9:e003066. DOI: 10.1136/jitc-2021-003066.

25. Sauder MB, et al. Canadian Skin Management in Oncology (CaSMO) Algorithm for Patients with Oncology Treatment-Related Skin Toxicities. *Skin Therapy Lett.* 2021; Suppl.

26. Cancer Care Ontario. Immune checkpoint inhibitor toxicity management. Toronto: Cancer Care Ontario; 2018. Available at: https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/ImmuneCheckpointInhibitor.pdf.

27. Ruggiero R, Balzano N, Di Napoli R, Fraenza F, Pentella C, Riccardi C, et al. Do peripheral neuropathies differ among immune checkpoint inhibitors? Reports from the European post-marketing surveillance database in the past 10 years. *Front Immunol.* 2023;16:1134436.

28. Kågedal M, Samineni D, Gillespie WR, Lu D, Fine BM, Girish S, et al. Time-to-event modeling of peripheral neuropathy: platform analysis of eight valine-citrulline-monomethylauristatin E antibody–drug conjugates. *CPT Pharmacometrics Syst Pharmacol.* 2019;8:606–15. DOI: 10.3389/fimmu.2023.1134436.

29. Shastri A, Al Aiyan A, Kishore U, Farrugia ME. Immune-mediated neuropathies: pathophysiology and management. *Int J Mol Sci.* 2023;24:7288. DOI: 10.3390/ijms24087288

30. BC Cancer. Symptom Management Guidelines: Chemotherapy-Induced Peripheral Neuropathy (CIPN). 2019. Available at: http://www.bccancer.bc.ca/nursing-site/Documents/15.%20Peripheral%20Neuropathy.pdf.

31. Mezzanotte JN, et al. Updates in the treatment of chemotherapy-induced peripheral neuropathy. *Curr Treat Options Oncol.* 2022;23:29–42. DOI: 10.1007/s11864-021-00926-0.

Notes

The Voice of Urology in Canada

Canadian Urological Association

The Voice of Urologic Oncology in Canada

Date of last update: April 18, 2025