



Positive Quality Intervention: Enfortumab Vedotin (Padcev®) Management for Advanced or Metastatic Urothelial Carcinoma

Description: The purpose of this PQI is to understand the management techniques and interventions when utilizing enfortumab vedotin.

Background: Enfortumab vedotin is a nectin-4 targeting antibody conjugated to the microtubule inhibitor monomethyl auristatin E (MMAE).¹ Enfortumab vedotin is approved by the FDA for the treatment of advanced or metastatic urothelial carcinoma in patients who have previously received a programmed death receptor (PD-1) or programmed death receptor (PD-L1) inhibitor and a cisplatin-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting.¹ More recently, the FDA expanded that approval to include patients who are cisplatin-ineligible and have received at least one prior line of systemic treatment.¹ In cohort 1 of the pivotal open-label phase II trial EV-201, patients were heavily pretreated and all had prior cisplatin treatment (50% received ≥ 3 prior treatments), and the objective response rate was 44%, including 12% complete responses.² Adverse effects were common, and 54% of patients had a grade ≥ 3 treatment-related adverse event, but these adverse events were manageable and no single grade ≥ 3 adverse event occurred in more than 10% of patients.² Treatment-related adverse effects led to dose reduction in 32% of patients and discontinuation in 12% of patients.² Cohort 2 of EV-201, published later, demonstrated the benefit of enfortumab vedotin specifically in patients who had not received cisplatin prior, with 52% of patients achieving an objective response and 20% with complete response.³ The phase III EV-301 trial confirmed the benefit of enfortumab vedotin compared to chemotherapy after treatment with cisplatin followed by immunotherapy (median overall survival, 12.88 vs. 8.97 months; hazard ratio for death, 0.70; 95% confidence interval, 0.56 to 0.89; $P=0.001$ with comparable incidence of treatment-emergent adverse events (93.9% in the enfortumab vedotin group and 91.8% in the chemotherapy group).⁴

PQI Process: Upon order of enfortumab vedotin administration

- Confirm appropriateness of enfortumab vedotin utilizing the EMR
- Review adverse events and interventions suggested as needed (see Supplemental Information: Table 1)
- Review dose specific adjustments as required (see Supplemental Information: Table 2)
- Drug interaction considerations¹
 - Enfortumab vedotin is metabolized via CYP3A4, and concomitant use of an antibody-drug conjugate containing MMAE and strong CYP3A4 inhibitors should be considered. Dose adjustment is typically not required

Patient Centered Activities:

- Advise patients that skin toxicities for enfortumab vedotin are likely to manifest as dry skin, pruritus, and/or maculopapular rash¹
 - Severe skin toxicities (10% incidence) included symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia¹
 - Boxed warning for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in first cycle
- Advise patients to self-monitor for peripheral sensory neuropathy and motor neuropathy. Sensory neuropathy (44%) was more common than motor (14%)^{1,2}
 - See [Chemotherapy Induced Peripheral Neuropathy](#) PQI
- Patient Assistance: [NCODA Financial Assistance Tool](#)

Important notice: NCODA has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. *Updated 1.14.22*



Supplemental Information:

Table 1: Selected Adverse Events and Suggested Interventions

| Event | Severity/Incidence | Suggested Intervention | Comments |
|-----------------|--|---|--|
| Skin Reactions | 54% (any grade) ¹ | Fragrance-free moisturizers/ointments Topical steroids and antihistamines as indicated Systemic steroids as indicated | Median time of onset for severe skin reactions was 0.8 months (range 0.2 – 5.3) ¹ Patients in EV-301 with grade 3 rash did not require treatment interruption if symptoms were manageable ⁴ |
| Hyperglycemia | 11% (any grade) ¹ regardless of known hyperglycemia at baseline 68% of patients with baseline hyperglycemia did not experience worsening | Blood glucose test prior to infusion – a basic metabolic panel suffices Does not need to be fasting | BMI and elevated A1c correlated to a higher incidence of grade 3/4 hyperglycemia ¹ Patients with baseline A1c ≥ 8% were excluded from EV-201 ² Patients with baseline A1c ≥ 6.5% should be referred to an appropriate provider for glucose management ¹ |
| Ocular Toxicity | Ocular disorders including blurred vision – 46% ¹ Dry eye symptoms – 36% ¹ | Consider prophylactic artificial tears ¹ Consider topical ophthalmic steroids after ophthalmic exams ¹ | Median time to onset for ocular disorders was 1.9 months (range 0.3 – 6.2) ¹ |
| Neuropathy | 49% (any grade). ¹ Peripheral sensory neuropathy was the most common reason for dose reduction | Recommend dose reduction as initial strategy Consider use of gabapentin or duloxetine | The median time to onset of grade ≥ 2 was 3.8 months (range: 0.6-9.2) At the last follow-up in EV-201, 19% had complete resolution and 26% had partial improvement. 76% had resolution or ongoing grade 1 neuropathy ² |
| Diarrhea | 42% (any grade) ¹ | Recommend anti-diarrheal medications for patient as required | Grade 4 diarrhea that resolves to grade ≤2 within 72 hours with supportive management does not require treatment interruption ⁴ |

Table 2: Dose Adjustments for Adverse Events¹

| | |
|--|--|
| Administration | IV infusion over 30 minutes on days 1, 8, 15 of a 28-day cycle until progression/toxicity |
| Starting dose | 1.25 mg/kg up to 125 mg* |
| First dose reduction | 1 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* |
| Renal/hepatic dysfunction considerations | No dose adjustment is required for renal dysfunction No current studies in <u>moderate</u> to <u>severe</u> hepatic dysfunction – consider avoiding use <u>Mild</u> hepatic dysfunction does not require an upfront dose reduction |

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| Adverse Event | Grade/Severity | Dose Modification |
|----------------------------------|-------------------------------|--|
| Hyperglycemia | Blood glucose > 250 mg/dL | Withhold until ≤ 250 mg/dL, then resume at same dose level |
| Peripheral neuropathy | 2 | Withhold until grade ≤ 1 , then resume at same dose level. If recurrence, withhold until Grade ≤ 1 , then resume and reduce one dose level |
| | ≥ 3 | Permanently discontinue |
| Skin reactions | 3 | Withhold until grade ≤ 1 , then resume at same dose level or consider reducing by one dose level |
| | 4 or recurrent 3 | Permanently discontinue |
| Other non-hematologic toxicities | 3 | Withhold until grade ≤ 1 , then resume at same dose level or consider reducing by one dose level |
| | 4 | Permanently discontinue |
| Hematologic toxicity | 3 or Grade 2 thrombocytopenia | Withhold until grade ≤ 1 , then resume at same dose level or consider reducing by one dose level |
| | 4 | Withhold until grade ≤ 1 , then resume and reduce one dose level or discontinue treatment |

*Based on actual body weight. Dose is capped for patients ≥ 100 kg

References:

1. Padcev® (enfortumab vedotin- ejfv) [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc.; March 2021.
2. Rosenberg JE, O'donnell PH, Balar AV, et al. Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy. *J Clin Oncol.* 2019;37(29):2592-2600.
3. Balar AV, McGregor BA, Rosenberg JE, et al. EV-201 Cohort 2: Enfortumab vedotin in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who received prior PD-1/PD-L1 inhibitors. *JCO.* 2021;39(6_suppl):394-394.
4. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. *N Engl J Med.* 2021;384(12):1125-1135.

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