Written By: Andrew Ruplin, PharmD
Fred Hutchinson Cancer Center

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

**Description:** The purpose of this PQI is to understand the management techniques and interventions related to the utilization of 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 as single agent for the treatment of advanced or metastatic urothelial carcinoma in patients who: 1) previously received a programmed death receptor (PD-1) or programmed death receptor ligand (PD-L1) inhibitor and a cisplatin-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting, or 2) are cisplatin-ineligible and have received at least one prior line of therapy.[1] More recently, the FDA expanded the approval for use in combination with pembrolizumab for patients with locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy based on results of the phase Ib/II EV-103/KEYNOTE-869 trial.[1,2] 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.[3] 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.[3] Treatment-related adverse effects led to dose reduction in 32% of patients and discontinuation in 12% of patients.[3] 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.[4] 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 between groups (93.9% in the enfortumab vedotin group and 91.8% in the chemotherapy group).[5] In EV-103, 45 patients between the dose escalation phase and dose expansion cohort A with cisplatin-ineligible disease and untreated locally advanced or metastatic urothelial cancer received enfortumab vedotin plus pembrolizumab until progression or toxicity.[2] After a median of 9 cycles, the objective response rate was 73.3% with a complete response rate of 15.6%.[2] The median overall survival and duration of response were 26.1 months and 25.6 months, respectively.[2] Some adverse events, such as peripheral neuropathy, occurred more often in combination treatment with pembrolizumab when compared to trials of enfortumab vedotin alone.[1]

**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 considerations[1]
    - Enfortumab vedotin is metabolized via CYP3A4, and concomitant use of an antibody-drug conjugate containing MMAE and dual P-gp and strong CYP3A4 inhibitors should be considered; dose adjustment is typically not required but may result in increased toxicities

**Patient-Centered Activities:**

- Advise patients that skin toxicities for enfortumab vedotin are likely to manifest as dry skin, pruritus, and/or maculopapular rash[1]

    - Severe (Grade 3-4) skin toxicities (12% incidence) included symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia and need to be evaluated urgently[1]
    - Boxed warning for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis
        - Most common in first cycle but may occur later in therapy
- Advise patients to self-monitor for and report peripheral sensory neuropathy and motor neuropathy. Sensory neuropathy (40%) was more common than motor (7%)[1]
    - See **Chemotherapy Induced Peripheral Neuropathy** PQI

- In combination with pembrolizumab: in EV-103/KEYNOTE-869, pembrolizumab was administered approximately 30 minutes after the end of enfortumab vedotin and this administration sequence is listed in the full prescribing information.[1] This may help delineate identification of patients who develop an infusion reaction to enfortumab vedotin versus pembrolizumab.[1,2]
- Skin and soft tissue reactions following infusion site extravasation occurred in 1.5% of patients across single agent trials and 0.3% of patients experienced Grade 3-4 reactions.[1] Symptoms worsened until 2-7 days after infusion and resolved within 1-4 weeks of the symptom peak. Monitor for infusion site extravasation and stop the infusion if it occurs.[1]
- Patient Assistance: **NCODA Financial Assistance Tool**

## References:


1. Padcev® (enfortumab vedotin- ejfv) [Prescribing Information].
2. Hoimes CJ, Flaig TW, Milowsky MI, et al. Enfortumab Vedotin Plus Pembrolizumab in Previously Untreated Advanced Urothelial Cancer. *J Clin Oncol*. 2023;41(1):22-31.
3. 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.
4. 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.
5. 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.


## Supplemental Information:

**Table 1: Selected Adverse Events and Suggested Interventions**

| Event | Severity/Incidence* | Suggested Intervention | Comments* |
|---|---|---|---|
| **Skin Reactions** | 56% (any Grade)[1] | Fragrance-free moisturizers/ointments, antihistamines, topical or systemic steroids as indicated | Median time of onset for severe skin reactions was 0.7 months (range 0.1 – 6)[1] |
| **Hyperglycemia** | 14% (any Grade) regardless of known hyperglycemia at baseline[1]<br>Baseline hyperglycemia or BMI ≥30 kg/m$^2$ were associated with a higher rate of treatment-emergent hyperglycemia[5] | Blood glucose test prior to infusion – as part of basic metabolic panel is appropriate<br>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 ≥ 6.5% should be referred to an appropriate provider for glucose management[1]<br>Patients with HbA1c ≥8% were excluded from clinical trials |
| **Ocular Toxicity** | Ocular disorders including blurred vision, keratitis, limbal stem cell deficiency, etc. – 40%[1]<br>Dry eye symptoms – 34%[1] | Consider prophylactic artificial tears[1] and consider topical ophthalmic steroids after eye exams[1] | Median time to onset for ocular disorders was 1.6 months (range 0 – 19)[1] |
| **Neuropathy** | 53% (any Grade)[1]<br>Peripheral sensory neuropathy was the most common reason for dose reduction | Recommend dose reduction as initial strategy to prevent worsening neuropathy | The median time to onset of Grade ≥ 2 for single agent was 4.9 months (range 0.1 – 20).[1] By time of final evaluation: 14% had total resolution, 46% partial improvement, 40% no improvement. Of |

| | | | |
|---|---|---|---|
| | With pembrolizumab: 65% any Grade, 45% Grade 2, 3.3% Grade 3[1,2] | Consider use of gabapentin or duloxetine for treatment of sensory neuropathy† | the 86% with residual symptoms, 51% had Grade ≥ 2[1] |
| **Diarrhea** | 24-45% (any Grade)[1,5] | Recommend as needed anti-diarrheal medications | Grade 4 diarrhea that resolves to Grade ≤ 2 within 72 hours with supportive management does not require discontinuation[5] |

* Data for single agent enfortumab vedotin unless otherwise noted
† Limited data for treatment of motor neuropathy

**Table 2: Dose Adjustments for Adverse Events[1]**

| | | |
|---|---|---|
| **Administration** | Single agent: IV infusion over 30 minutes on days 1, 8, 15 of a 28-day cycle until progression/toxicity | |
| | In combination with pembrolizumab: IV infusion over 30 minutes on days 1 and 8 of a 21-day cycle until progression/toxicity. Pembrolizumab should be administered over 30 minutes on day 1 of each cycle approximately 30 minutes following the end of the enfortumab vedotin infusion. | |
| **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** | No dose adjustment is required for renal dysfunction<br>No current studies in moderate to severe hepatic dysfunction (total bilirubin >1.5 x ULN and AST any) – consider avoiding | |
| | | |
| **Adverse Event** | **Grade/Severity** | **Dose Modification** |
| **Hyperglycemia** | Blood glucose > 250 mg/dL | Hold until ≤ 250 mg/dL, then resume at same dose level |
| **Peripheral neuropathy** | 2 | Hold until Grade ≤ 1, then resume at same dose level or reduced by one level |
| | ≥ 3 | Permanently discontinue |
| **Skin reactions** | 3 | Hold until Grade ≤ 1, then resume at same dose level or reduced by one level |
| | 4 or recurrent 3 | Permanently discontinue |
| **Other non-hematologic toxicities** | 3 | Hold until Grade ≤ 1, then resume at same dose level or reduced by one level |
| | 4 | Permanently discontinue |
| **Hematologic toxicity** | 3 or 2 thrombocytopenia | Hold until Grade ≤ 1, then resume at same dose level or reduced by one level |
| | 4 | Hold until Grade ≤ 1, then resume at same dose level or reduced by one level |
| **Pneumonitis** | 2 | Hold until Grade ≤ 1 for persistent or recurrent Grade 2, consider dose reduction by one level |
| | ≥ 3 | Permanently discontinue |

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