Written By: Andrew Ruplin, PharmD
Fred Hutchinson Cancer Center & UW Medicine

Positive Quality Intervention: Enfortumab Vedotin-ejfv (Padcev®) and Pembrolizumab (Keytruda®) 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 the combination treatment of enfortumab vedotin-ejfv and pembrolizumab.

Background: Enfortumab vedotin-ejfv (EV) is a nectin-4 targeting antibody conjugated to the microtubule inhibitor monomethyl auristatin E (MMAE) which first received accelerated approval in 2019 as monotherapy for the treatment of locally advanced or metastatic (LA/m) urothelial cancer that had been previously treated with cisplatin-containing chemotherapy and programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.[1] Over subsequent years, additional clinical trials studying monotherapy or in combination with the PD-1 inhibitor pembrolizumab confirmed the survival benefits of EV in the locally advanced/metastatic setting.[2-6] This led first to the approval of combination EV and pembrolizumab for patients ineligible to receive cisplatin-containing chemotherapy for initial treatment of LA/m urothelial cancer based on results from the EV-103/KEYNOTE-869, followed by the landmark approval of this combination as initial therapy without stipulation for LA/m urothelial cancer based on survival benefits seen in the pivotal open-label randomized EV-302/KEYNOTE-A39 trial in which EV-pembrolizumab was studied as frontline therapy versus platinum (cisplatin or carboplatin) plus gemcitabine.[5-6] EV-pembrolizumab is now considered a preferred first-line treatment option for LA/m urothelial cancer.

PQI Process: Upon order of EV-pembrolizumab

- Confirm appropriateness of EV-pembrolizumab utilizing the EMR
    - EV-pembrolizumab is currently approved by the FDA to treat locally advanced or metastatic urothelial cancer
    - Testing for nectin-4 or PD-L1 expression is not required and is not used for treatment decisions
    - EV is also approved as a single agent to treat LA/m urothelial cancer after platinum-containing chemotherapy and immune checkpoint inhibitor or following one or more prior lines of therapy in cisplatin-ineligible patients. Please see the PQI Enfortumab Vedotin-ejfv (Padcev) Management for Advanced or Metastatic Urothelial Carcinoma for discussion of single-agent EV
    - Review dose specific adjustments as required (see Supplemental Information: Table 2)
    - Drug interaction considerations[1]
        - The MMAE portion of EV is metabolized via CYP3A4, and concomitant use of an antibody-drug conjugate containing MMAE with dual P-gp and/or strong CYP3A4 inhibitors should be considered; dose adjustment is typically not required and has not been studied but this interaction may result in increased toxicities.
        - Pembrolizumab drug interactions are not definitively known, but medications that suppress the immune system such corticosteroids are hypothesized to interfere with pembrolizumab efficacy and should be limited as much as possible.

Patient-Centered Activities:

- Administer appropriate anti-emetics for pre-medication. Across trials, fewer than 20% of patients treated with enfortumab vedotin experienced vomiting.[1] Among patients who had vomiting, <5% had severe (Grade 3-4) vomiting[2]

Written By: Andrew Ruplin, PharmD
Fred Hutchinson Cancer Center & UW Medicine

- The most common treatment-related adverse events of any grade with frequency ≥ 20% with combination EV-pembrolizumab in EV-103/KEYNOTE-869 and EV-302/KEYNOTE-A39 trials included peripheral sensory neuropathy (56, 50%), pruritus (33, 40%), alopecia (49, 33%), maculopapular rash (36, 33%), fatigue (51, 29%), diarrhea (47, 28%), decreased appetite (40, 27%), nausea (29, 20%), dysgeusia (33%), weight decreased (24%), dry skin (22%), ALT/AST increased (20%), and anemia (20, 14%)[5,6]
- Due to the diversity of timing, severity, and manifestation of immunotherapy-related adverse events (IrAEs), patients reporting symptoms should be carefully evaluated to appropriately distinguish between IrAEs and EV adverse events, the latter of which are caused by on-target and off-target effects of the cytotoxic payload MMAE and may require different intervention from an IrAE
    - Please see PQI Enfortumab Vedotin-ejfv (Padcev) Management for Advanced or Metastatic Urothelial Carcinoma for suggested interventions for adverse events associated with EV
    - Please see Immune-Related Adverse Event (irAE) Management Tool - NCODA
- Advise patients to self-monitor for and report symptoms of peripheral neuropathy. Sensory neuropathy (38%) was more common than motor (7%) with EV monotherapy. EV-pembrolizumab combination has shown a higher incidence of peripheral neuropathy compared to EV monotherapy (67% vs 53%, respectively).[1] Neuropathy may resolve over time, but 87% of patients (N = 373) evaluated for resolution had residual neuropathy[1]
    - See Chemotherapy Induced Peripheral Neuropathy PQI
- Advise patients that skin toxicities for EV are likely to manifest as dry skin, pruritus, and/or maculopapular rash
    - Consider topical corticosteroids and antihistamines as initial management of Grade 1-2 skin toxicities as clinically indicated[1,7]
    - Severe (Grade 3-4) skin toxicities (17% incidence with EV + pembro; 14% for EV monotherapy) included symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia and need to be evaluated urgently
        - EV has a black box warning for Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
            - Most common in first cycle but may occur later in therapy
        - Discontinue treatment if SJS or TEN are confirmed, or if or Grade 4 or recurrent Grade 3 skin reactions occur
- In EV-103/KEYNOTE-869 and EV-302/KEYNOTE-A39, pembrolizumab was administered approximately 30 minutes after completion of EV and this administration strategy is listed in the full prescribing information for pembrolizumab.[5-7] Subsequent doses after cycle 1 day 1 in EV-302/KEYNOTE-A39 were administered with a delay of 15 minutes if the first infusion was well-tolerated. This practice may help delineate identification of patients who develop an infusion reaction to EV versus pembrolizumab.[1,2] It is unknown if there is any clinical significance to this practice compared to back-to-back administration without delay.
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. Padcev® (enfortumab vedotin-ejfv) [prescribing information].
2. Yu EY, Petrylak DP, O'Donnell PH, 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(6):872-882.
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. J Clin Oncol. 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.

5. 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.
6. Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. N Engl J Med. 2024;390(10):875-888.
7. Keytruda® (pembrolizumab) [prescribing information].

Supplemental Information:

Table 1: Withholding or Discontinuing Treatment based on Adverse Events

Enfortumab Vedotin		
Adverse Event	**Grade/Severity**	**Dose Modification**
Hyperglycemia	Blood glucose > 250 mg/dL	Hold until ≤ 250 mg/dL, then resume at same dose level
Pneumonitis/Interstitial Lung Disease	2	Hold until Grade ≤ 1, then resume at same dose level or consider reduction by one level
	≥ 3	Permanently discontinue
Peripheral neuropathy	2	For 1st occurrence, hold until Grade ≤ 1, then resume at same dose level. For recurrence, hold until Grade ≤ 1, then resume reduced by one level
	≥ 3	Permanently discontinue
Skin reactions	Persistent or recurrent Grade 2	Consider holding until Grade ≤ 1, then resume at same dose level or reduced by one level
	3	Hold until Grade ≤ 1, then resume at same dose level or reduced by one dose level
	Suspected SJS or TEN	Immediately hold, consult a specialist to confirm diagnosis. If not SJS/TEN, see Grade 2-4 skin reactions.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue
Other non-hematologic toxicities	3	Hold until Grade ≤ 1, then resume at same dose level or reduced by one dose 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
Pembrolizumab		
IrAEs are diverse and potentially complex. Conscientious evaluation should be performed for any symptom to evaluate for a possible autoimmune-like etiology elicited by immunotherapy. Clinicians should consider review of consensus guidelines for work-up and management of IrAEs. In general, consider discontinuing pembrolizumab for: 1) Grade 4 IrAEs, 2) recurrent Grade 3 IrAEs, or 3) recurrent Grade 3 IrAEs require systemic immunosuppressive treatment or an inability to reduce corticosteroid dose to 10 mg or less of prednisone/equivalent per day within 12 weeks of beginning steroids. There are no agreed-upon dose modifications for toxicity.		

Written By: Andrew Ruplin, PharmD
Fred Hutchinson Cancer Center & UW Medicine

Table 2: Dosing and Modifications

Administration		21-day cycle until disease progression or intolerable toxicity: • EV: IV infusion over 30 minutes on days 1 and 8 • Pembrolizumab: IV infusion over 30 minutes on day 1
Enfortumab Vedotin	**Initial 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 No current studies in moderate to severe hepatic dysfunction (total bilirubin >1.5 x ULN and AST any) – consider avoiding or close adverse event monitoring if treatment is used
Pembrolizumab	**Initial Dose**	200 mg
	Dose adjustments	There are no known dose adjustments for pembrolizumab for toxicity or renal/hepatic dysfunction. Metabolism of pembrolizumab is unaffected by renal/hepatic function. The FDA has approved 400 mg every 6 weeks as single-agent treatment in urothelial cancer but not combined with EV. All trials of combination treatment with EV have used 200 mg every 3 weeks.

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