Enfortumab Vedotin-ejfv (PADCEV)
National Drug Monograph Addendum
November 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

Background

In the setting of metastatic urothelial carcinoma, cisplatin based chemotherapy is the standard of care that is recommended by both the VA Clinical Pathways and the National Comprehensive Cancer Network (NCCN) alike. Unfortunately, many patients encountered in clinical practice will be classified as cisplatin-ineligible, thus alternative therapies must be considered. What classifies a patient as cisplatin-ineligible is often clinical judgment, however tools have been develop to standardize this process. One tool that is frequently used is the Galskey criteria.[1] This tool consists of five criteria and if a patient meets any of them they would be considered ineligible for cisplatin based therapy. These criteria include the following: creatinine clearance <60 ml/min, New York Heart Association (NYHA) Class III or higher, Grade-2 or higher peripheral neuropathy or hearing impairment, or an Eastern Cooperative Oncology Group (ECOG) performance status ≥2.

Alternative treatment modalities have been evaluated in the setting of cisplatin-ineligibility however options are limited. On April 3, 2023, Enfortumab Vedotin received accelerated approval by the FDA for use as first line therapy in combination with pembrolizumab for metastatic urothelial carcinoma in patients ineligible for cisplatin based therapy. Previously, this agent had only been approved as monotherapy following disease progression after at least one prior line of chemotherapy or immunotherapy. This represents a new alternative treatment option that has already become incorporated in clinical guidelines.

Efficacy

Trial	Inclusion/Exclusion	Patients	Intervention and Comparator	Outcomes
EV-103 Trial Cohort K[2]	Inclusions • Age ≥ 18 years • Confirmed locally advance/metastatic urothelial carcinoma • ECOG performance status 0-2 • Ineligible for cisplatin-based chemotherapy Exclusions • Previous systemic treatment for local or systemic disease within 12-months • Preexisting grade 2 or higher neuropathy • Active central nervous system disease involvement • Uncontrolled diabetes (HbA1c ≥8% or 7-8% with presence of diabetic symptoms)	N = 151	Combination Group N = 77 Enfortumab vedotin 1.25 mg/kg (maximum 125mg) IV over 30 minutes on Days 1 & 8 of a 21 day cycle Pembrolizumab 200mg IV on day 1 of a 21 day cycle Single Agent Group N = 73 Enfortumab vedotin 1.25 mg/kg (maximum 125mg) IV over 30 minutes on Days 1 & 8 of a 21 day cycle	Combination vs Single Agent Objective Response: • 64.5% (95% CI, 52.7-75.1) vs 45.2% (95% CI, 33.5-57.3) Duration of Response: • NR vs 13.2 months
EV-103 Trial Cohort A[3] **(Dose Escalation)**	Inclusions • Age ≥ 18 years • Confirmed locally advance/metastatic urothelial carcinoma • ECOG performance status 0-1 • Expected life expectancy ≥3 months • Adequate organ function	N = 45	Single Arm Enfortumab vedotin 1.25 mg/kg (maximum 125mg) IV over 30 minutes on Days 1 & 8 of a 21 day cycle	Complete response: 15.6% Partial response: 57.8% Median Progression Free Survival: 12.3 months Median Overall Survival: 26.1 months

	• Eligible for treatment with Pembrolizumab Exclusions • Preexisting grade 2 or higher neuropathy • Active central nervous system disease involvement • Uncontrolled diabetes		Pembrolizumab 200mg IV on day 1 of a 21 day cycle	

EV-103 Trial Cohort K

- Baseline characteristics were similar between the two treatment arms.
- Primary endpoint of objective response rate was assessed by a blinded independent central review (BICR).
- Secondary endpoints were assessed by the investigators.
- Statistical comparison was not performed between the treatment arms; Enfortumab vedotin monotherapy was included to assess its contribution to the response rate
- The median follow-up in the combination arm was 14.8 months and 15.0 months in the monotherapy arm.
- Prespecified subgroups (including PD-L1 expression) were consistent with overall ORR.

Safety

Study	Results – (Enfortumab + Pembrolizumab vs Enfortumab)
EV-103 Trial Cohort K	**Grade ≥ 3 TRAE:** 63.2% vs 47.9% **Serious TRAE:** 23.7% vs 15.1% **TRAE leading to death:** 3.9% vs 2.7% **TRAE leading to discontinuation** - **Pembrolizumab:** 22.4% - **Enfortumab vedotin:** 25.0% vs 19.2% - **Both:** 5.3%
EV-103 Trial Cohort A	**Serious TRAE:** 15.6% **TRAE Leading to dose reductions:** 31.1% **TRAE leading to discontinuation**: 24.4%

TRAE: Treatment Related Adverse Events

- **Boxed warnings:**
  - No new boxed warning with combination
- **Contraindications:**
  - No new contraindications with combination
- **Other Warnings / Precautions:**
  - Skin reactions including severe skin reactions may be more common when Enfortumab vedotin is used in combination with Pembrolizumab.
  - Enfortumab may cause severe or life-threatening inflammation of the lungs that can lead to death. These severe problems may happen more often when Enfortumab vedotin is given in combination with Pembrolizumab.
  - Nerve problems may happen more often when Enfortumab vedotin is given in combination with Pembrolizumab.
- **Other Considerations:**
  - In the setting of metastatic urothelial carcinoma, there are very few therapeutic options with high quality data. The combination of Enfortumab vedotin with Pembrolizumab has demonstrated efficacy in cisplatin-ineligible patients. There is no data directly comparing the combination of Enfortumab vedotin and Pembrolizumab to any of the alternative options. When looking at the outcomes of each study independent of one another, there is a notable difference in OS. However, it should be stated that the patient populations are not directly comparable, and confounding variables could be one of many explanations for this difference.

- The addition of Pembrolizumab to Enfortumab vedotin introduces additional toxicities. No direct comparisons have been made comparing the combination Enfortumab vedotin with Pembrolizumab to the alternatives of single agent Pembrolizumab or Gemcitabine plus Carboplatin.

Alternative Treatments

Table 1 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Gemcitabine plus Carboplatin	F	• Metastatic Bladder Cancer Stage IVB – Cisplatin Ineligible – VA Clinical Pathways • NCCN Category 1 Recommendation – Cisplatin Ineligible	• VA Pathway criteria for cisplatin ineligibility – defined as ECOG=2, creatinine clearance > 30 and < 60 mL/min, hearing loss/dysfunction Phase II/III Data[4] • ORR 41.2% (CR: 3.4% PR: 37.8%) • OS: 9.3 months • Similar outcomes to M-CAVI (Methotrexate/Carboplatin/Vinblastine) but better tolerated • Rates of severe acute toxicity: 9.3% vs 21.2%)
Pembrolizumab	F	• Metastatic Bladder Cancer Stage IVB – Cisplatin Ineligible & Ineligible for Chemotherapy – VA Clinical Pathways • NCCN Category 1 Recommendation – Cisplatin Ineligible	• VA Pathway criteria for cisplatin ineligibility – defined as ECOG=2, creatinine clearance > 30 and < 60 mL/min, hearing loss/dysfunction • For patients who are ineligible for chemotherapy Phase II Data[5] • ORR: 24% (95% CI 20-29) • CR: 5% PR: 19% • Cisplatin-ineligible patients

Conclusions

- Cohort K of the EV-103 Trial demonstrated that combination enfortumab vedotin with pembrolizumab is a safe and effective first line option for patients with metastatic urothelial carcinoma.
- Rates of grade ≥3 toxicity were higher with the combination, however rates of treatment related adverse events were similar.
- Patients who are ineligible for cisplatin based therapy have limited treatment options. This combination regimen is another option to meet the unmet needs of these patients.
- The VA Clinical Pathways have been updated to include enfortumab vedotin plus pembrolizumab as an option for patients who are determined to be ineligible for cisplatin. Single agent enfortumab vedotin is still listed as an option for patients who have progressed on at least one other line of systemic therapy.
- Recommend the addition of the Enfortumab vedotin to the national formulary with PA-F

Outcome in clinically significant area	Objective response (CR or PR): 64.5%
Effect Size	n/a
Potential Harms	Grade ≥ 3 Treatment related adverse events 63.2%
Net Clinical Benefit	n/a

References:

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