American Society of Clinical Oncology
May 29–31, 2020
Abstract No. TPS5092

Study EV-103: New Randomized Cohort Testing Enfortumab Vedotin as Monotherapy or in Combination with Pembrolizumab in Locally Advanced or Metastatic Urothelial Cancer (Trial in Progress)

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Background

There remains high unmet need in first-line (1L) locally advanced or metastatic urothelial carcinoma (la/mUC), particularly for patients who are ineligible for cisplatin-based therapies.

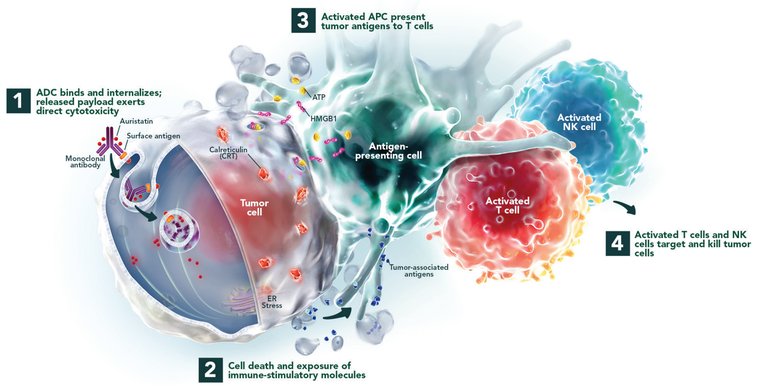
- Platinum-based chemotherapy ± programmed death-ligand 1 (PD-L1) inhibitor has demonstrated modest objective response rates (ORR) and limited durability, reinforcing the urgent unmet need in the 1L setting for patients with la/mUC.[1]
- Cisplatin-based chemotherapy is the standard for 1L patients with la/mUC; however nearly half of the patients are excluded from this treatment due to renal dysfunction, neuropathy, or poor performance status.[2]
- Enfortumab vedotin-ejvf (EV) recently received FDA accelerated approval* based on tumor response rates for adults with la/mUC, who have previously received a programmed cell death protein 1 (PD-1)/PD-L1 inhibitor and a platinum-containing therapy.
- In the ongoing phase 1b/2 study EV-103/KEYNOTE-869 (NCT03288545), the safety and antitumor activity of EV are investigated as monotherapy (for the first time in the 1L setting) and with PD-1 inhibitor pembrolizumab and/or chemotherapy in la/mUC.
- The EV + pembrolizumab regimen demonstrates encouraging and durable activity (ORR 73.3%, Median PFS 12.3 mo, and 93% had reduction in target lesions) and has a tolerable and stable safety profile in cisplatin-ineligible patients with la/mUC in the 1L setting (Abstract 5044).
- The combination of enfortumab vedotin and pembrolizumab was granted Breakthrough Therapy Designation for cisplatin ineligible patients with la/mUC in 1L setting by the FDA on 18 Feb 2020.

*Adults with locally advanced or metastatic urothelial cancer who have previously received a PD-1/PD-L1 inhibitor and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting. This indication is approved under accelerated approval based on tumor response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Rationale for Enfortumab Vedotin + Pembrolizumab Combination

Hypothesis for Vedotin ADCs and Immunogenic Cell Death

- EV, an antibody-drug conjugate (ADC), delivers the microtubule-disrupting agent monomethyl auristatin E (MMAE) to cells expressing Nectin-4, which is highly expressed in urothelial carcinoma.[2,3]
- Enfortumab vedotin and pembrolizumab each have single agent activity in la/mUC in advanced lines of therapy.
- Preclinical studies show that antibody-drug conjugates (brentuximab vedotin, ladiratuzumab vedotin, and tisotumab vedotin)[4-7] linked to MMAE induce immunogenic cell death and may enhance antitumor immunity.
- Clinical data suggests the combination of enfortumab vedotin + pembrolizumab may have the potential to induce greater antitumor activity in la/mUC compared with either agent alone.[8]

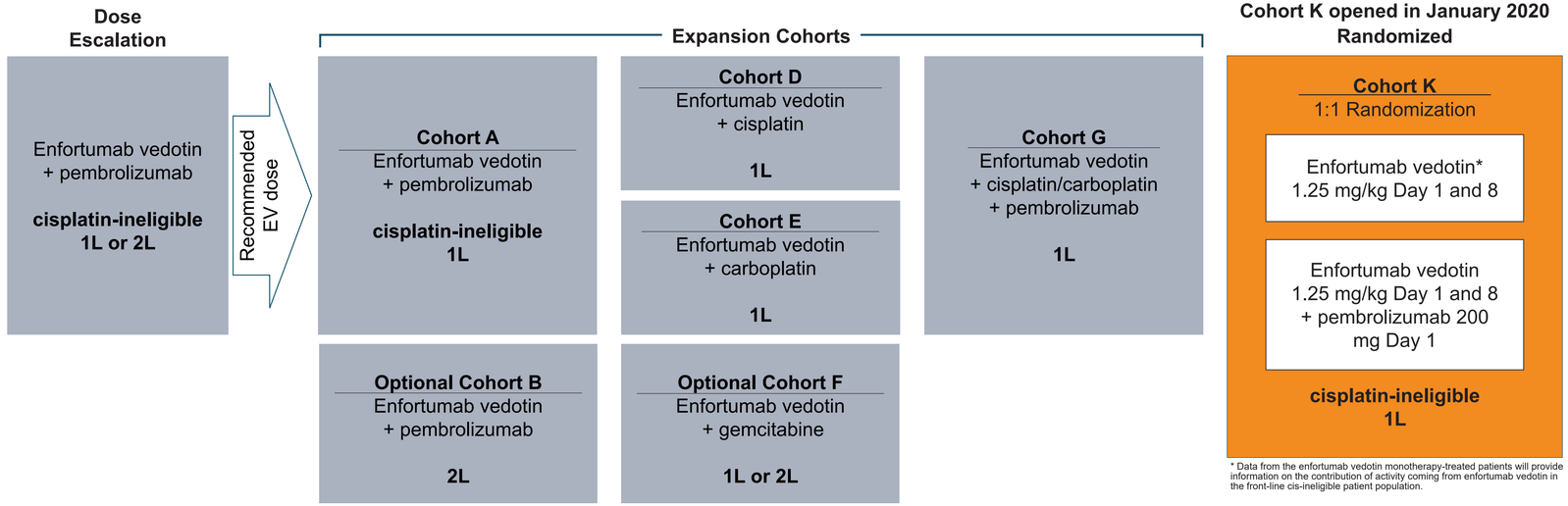


Antibody-drug conjugates are investigational agents, and their safety and efficacy have not been established.

Disclosures: This study was funded by Seattle Genetics, Inc., Astellas Pharma, Inc., and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. TWF2, TWF4, MAB, AVB, EH, SS, JER, DPP, EFB, JRM, and MIM received research funding from Seattle Genetics, Inc./Astellas Pharma, Inc. TWF4, AVB, SS, DPP, and MIM received research funding from Merck & Co., CJH received funding from Merck, Sharp & Dohme, Inc., STT holds a consulting and advisory role with Astellas Pharma, Inc. CJH, MAB, AVB, JER, and DPP hold a consulting or advisory role with Seattle Genetics, Inc. TWF2 and CJH received honoraria from Seattle Genetics, Inc. TWF2 received honoraria from Astellas Pharma, Inc., and AVB received honoraria from Merck & Co. ASC is an employee of and has an ownership interest in Seattle Genetics, Inc. JLS is an employee of Astellas Pharma, Inc. MFC is an employee of and has an ownership interest in Merck & Co., Inc.

EV-103 Cohort K is now enrolling cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer. Patients will receive either enfortumab vedotin monotherapy or enfortumab vedotin plus pembrolizumab in the first-line setting to further evaluate this potential platinum-free option.

EV-103 Study Design for Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC) Cohorts



* Data from the enfortumab vedotin monotherapy-treated patients will provide information on the contribution of activity coming from enfortumab vedotin in the front-line cis-ineligible patient population.

Cohort K Objectives

Primary Objectives

- To assess the antitumor activity of enfortumab vedotin monotherapy and enfortumab vedotin in combination with pembrolizumab as measured by ORR per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by blinded independent central review.

Secondary Objectives

- To assess the following parameters:
  - ORR per RECIST 1.1 by investigator assessment
  - Duration of response per RECIST 1.1
  - Disease control rate per RECIST 1.1
  - Progression free survival (PFS) per RECIST 1.1
  - Overall survival
  - Safety and tolerability of enfortumab vedotin monotherapy or enfortumab vedotin in combination with pembrolizumab

Cohort K Eligibility

Key Criteria

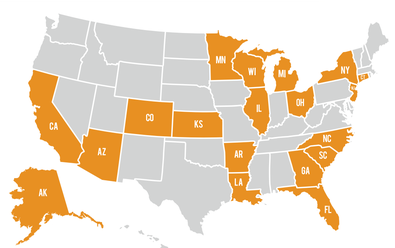
- Ineligible for cisplatin-based chemotherapy due to at least 1 of the following:
  - Glomerular filtration rate <60mL/min and ≥30 mL/min
  - Eastern Cooperative Oncology Group (ECOG) performance status of 2
  - National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE) Version 4.03 Grade ≥2 hearing loss
  - New York Heart Association (NYHA) Class III heart failure
- No prior systemic treatment for locally advanced or metastatic disease.
- No adjuvant/neoadjuvant platinum-based therapy within 12 months prior to randomization.

Response Assessments

- Objective responses will be confirmed per RECIST 1.1 with repeat scans at least 4 weeks after the first documentation of response.
- After radiographically confirmed disease progression on or following study treatment or initiation of new anticancer therapy, patients will be followed every 12 weeks to obtain information on subsequent anticancer therapy and to assess survival status.

Study Sites

- 27 active sites around the US



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