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Study EV-302: A 3-Arm, Open-Label, Randomized Phase 3 Study of Enfortumab Vedotin Plus Pembrolizumab and/or Chemotherapy, Versus Chemotherapy Alone, in Untreated Locally Advanced or Metastatic Urothelial Cancer

Michiel S. van der Heijden[1], Shilpa Gupta[2], Matthew D. Galsky[3], Christina Derleth[4], Joyce Steinberg[5], Ritesh Kataria[6], Thomas Powles[7]

[1]The Netherlands Cancer Institute, Amsterdam, the Netherlands; [2]Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH, USA; [3]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [4]Seattle Genetics, Inc., Bothell, WA, USA; [5]Astellas Pharma, Inc., Northbrook, IL, USA; [6]Merck & Co., Inc., Kenilworth, NJ, USA; [7]Barts Cancer Institute, Queen Mary University of London, London, UK

Unmet Need for Treatment of Locally Advanced/Metastatic Urothelial Cancer

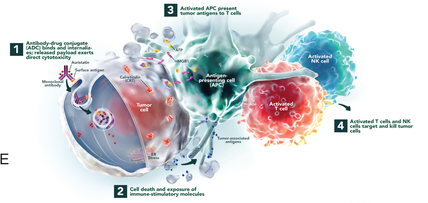
- Bladder cancer, the most common form of urothelial cancer (UC), is estimated to kill nearly 200,000 patients globally on an annual basis, including more than 65,000 in Europe[1,2]
- The 5-year relative survival rate for distant metastatic disease is approximately 5%[3]
- Cisplatin-based chemotherapy is the standard of care for locally advanced (la)/metastatic (mUC) in the first-line setting for eligible patients[4]. However, more than 50% of patients are cisplatin-ineligible[5]
- In the US and Europe, first-line use of programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) inhibitors is limited to cisplatin-ineligible patients with high PD-L1 expression. Additionally, the US approval includes platinum-ineligible, first-line patients.
- In Dec 2019, US FDA granted accelerated approval for enfortumab vedotin monotherapy in patients who previously received prior PD-1/PD-L1 inhibitors and platinum-containing chemotherapy in the neoadjuvant/adjuvant or la/metastatic setting (EV-201 Cohort 1)
- The FDA has granted Breakthrough Therapy Designation to enfortumab vedotin + pembrolizumab for the treatment of la/mUC in cisplatin-ineligible patients in the first-line setting based on data from the ongoing phase 1b/2 study EV-103
  - Preliminary results from cisplatin-ineligible patients treated with enfortumab vedotin + pembrolizumab in the first-line setting showed an objective response rate (ORR) of 73.3%, median progression-free survival (PFS) of 12.3 months, and median overall survival (OS) not yet reached[6]
  - The safety profile was manageable and no new safety signals were identified[6]
  - Enfortumab vedotin + pembrolizumab activity was seen regardless of PD-L1 expression[6]
- The ongoing, pivotal, randomized EV-103 Cohort K will further evaluate enfortumab vedotin + pembrolizumab versus enfortumab vedotin monotherapy in cisplatin-ineligible patients in the first-line setting

Enfortumab Vedotin is an Investigational Antibody-Drug Conjugate Directed at Nectin-4

- Enfortumab vedotin consists of a Nectin-4 directed fully human monoclonal antibody and the microtubule-disrupting agent monomethyl auristatin E (MMAE), conjugated by a protease-cleavable linker.
- Nectin-4 is a transmembrane cell adhesion molecule[7] expressed in multiple tumor types, including UC[8]
- In the EV-201 monotherapy clinical trial:
  - 100% of the UC patient tumor samples tested expressed Nectin-4[9]
  - Activity was seen regardless of Nectin-4 and PD-L1 expression[9]

Rationale for Combining MMAE-ADC + Pembrolizumab

- Enfortumab vedotin and pembrolizumab each have single agent activity in la/mUC
- Preclinical studies show that antibody-drug conjugates (brentuximab vedotin, ladiratuzumab vedotin, and tisotumab vedotin)[10-13] 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 to either agent alone

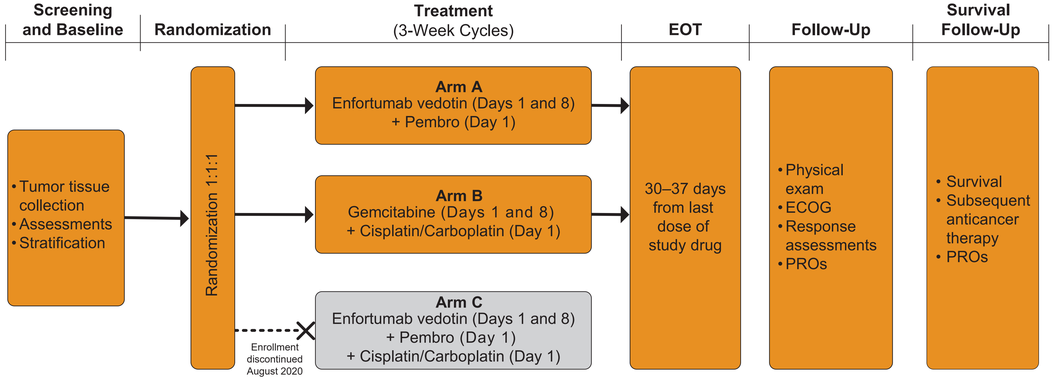


Antibody-drug conjugates are investigational agents, and their safety and efficacy have not been established.

EV-302 Study Design and Rationale

- EV-302 (NCT04223856; EudraCT Number 2019-004542-15) began as a global 3-arm, open-label, randomized phase 3 study evaluating the efficacy and safety of the following treatment arms in patients with unresectable, previously untreated la/mUC:
  - Arm A: Enfortumab vedotin + pembrolizumab, **or**
  - Arm C: Enfortumab vedotin + cisplatin or carboplatin + pembrolizumab, **versus**
  - Arm B: Gemcitabine + cisplatin or carboplatin
- Study drugs were administered at the following doses:
  - Enfortumab vedotin: 1.25 mg/kg (no maximum # of cycles)
  - Pembrolizumab: 200 mg (maximum of 35 cycles)
  - Gemcitabine: 1000 mg/m²
  - Cisplatin: 70 mg/m²
  - Carboplatin: AUC 4.5 or 5

  (maximum of 6 cycles each)
- Arm C enrollment discontinued in August 2020 per sponsors' decision based on data and the changing landscape:
  - Recent outcomes of KEYNOTE-361 and IMvigor130 suggest limited clinical benefit for the triplet combinations of platinum, gemcitabine and PD-1/PD-L1 inhibitors in first-line mUC[14,15]
  - Enfortumab vedotin + pembrolizumab demonstrated rapid and durable activity, promising survival, and tolerable safety in EV-103[9]
- EV-302 will continue to evaluate the efficacy and safety of enfortumab vedotin + pembrolizumab (Arm A) versus gemcitabine + cisplatin or carboplatin (Arm B)
- Approximately 760 patients will be enrolled in EV-302



EOT= End of Treatment; Pembro=pembrolizumab; PROs=patient reported outcomes

- Stratification Factors for Randomization: cisplatin eligibility (eligible/ineligible), liver metastases (present/absent), PD-L1 expression (high/low)
- Follow-up until disease progression, death, consent withdrawal, or study closure

Objectives

Primary Objectives

- To compare PFS between the experimental Arm A and the control Arm B per RECIST v1.1 by blinded independent central review (BICR)
- To compare OS between Arm A and Arm B

Secondary Objectives

- To evaluate the ORR, duration of response, and disease control rate between Arm A and Arm B per RECIST v1.1 by BICR and investigator assessment
- To evaluate PFS per investigator assessment between Arm A and Arm B
- To assess the impact of study treatment on quality of life (QOL), and symptoms including pain from the subject perspective
- To evaluate the safety profile of each treatment regimen

Response Assessments

- Computed tomography (CT) scans with contrast (unless contraindicated) every 9 weeks (±1 week) from the randomization date for the first 18 months, then every 12 weeks (±1 week) thereafter
- Objective responses will be confirmed per RECIST v1.1
- Assessments will continue until radiologically-confirmed disease progression per RECIST v1.1 as determine by BICR, death, consent withdrawal, or study closure

Eligibility

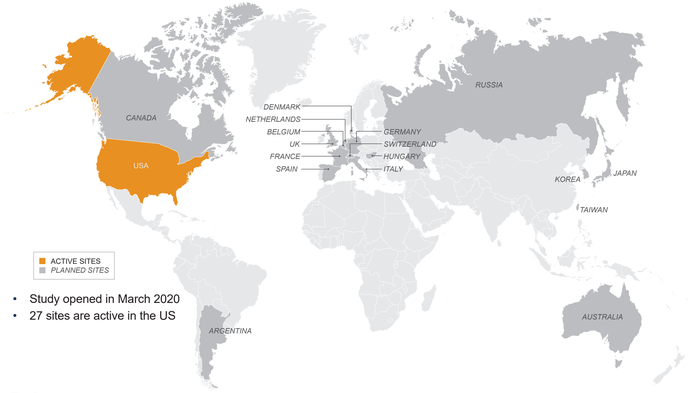
Key Inclusion Criteria

- Histologically documented, unresectable, la/mUC
- Measurable disease by investigator assessment per RECIST v1.1
- ≥18 years of age with >12 weeks life expectancy
- No prior systemic therapy except for neoadjuvant or adjuvant (with cystectomy) chemotherapy with recurrence >12 months after therapy completion
- Adequate hematologic and organ function tests
- ECOG performance status of 0, 1, or 2
- Eligible to receive cisplatin- or carboplatin-based chemotherapy and pembrolizumab by investigator judgement
- Adequate available archival tumor tissue or ability to undergo a new tumor biopsy

Key Exclusion Criteria

- Previous treatment with enfortumab vedotin, other MMAE-based antibody-drug conjugates, or PD-1/PD-L1 inhibitors
- Ongoing sensory or motor neuropathy ≥ Grade 2
- Active CNS metastases
- Uncontrolled diabetes
- Currently receiving systemic antimicrobial treatment for active infection or high dose steroids
- History of another malignancy within 3 years or evidence of residual disease from previously diagnosed malignancy

Study Sites



- Study opened in March 2020
- 27 sites are active in the US

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