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STUDY EV-302: A 2-ARM, OPEN-LABEL, RANDOMIZED CONTROLLED PHASE 3 STUDY OF ENFORTUMAB VEDOTIN IN COMBINATION WITH PEMBROLIZUMAB VS CHEMOTHERAPY IN PREVIOUSLY UNTREATED ADVANCED UROTHELIAL CARCINOMA (TRIAL IN PROGRESS)

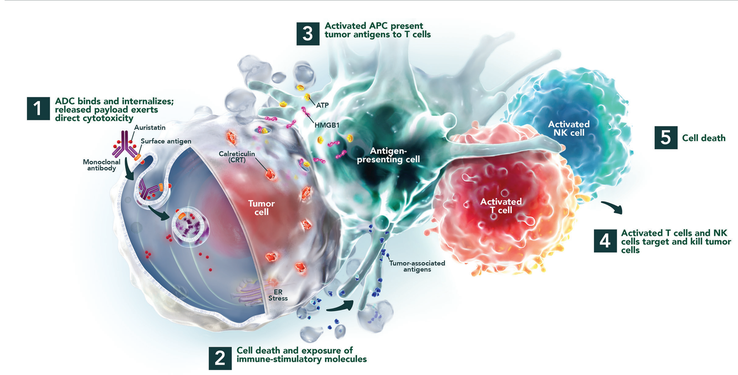
Michiel S. van der Heijden[1], Shilpa Gupta[2], Matthew D. Galsky[3], Christina Derleth[4], Sue Lee[5], Ritesh Kataria[6], Thomas Powles[7]

[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]Seagen 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

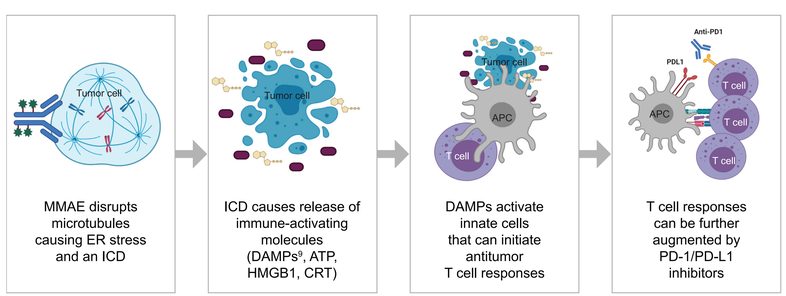
Background

- Even with advances in this setting, 5-year OS is still ~6%, thus more effective and tolerable treatment options are needed in the 1L setting for previously untreated la/mUC[1,2]
- EV is a Nectin-4 directed ADC comprised of a fully human monoclonal antibody conjugated to the microtubule-disrupting agent, MMAE, via a protease-cleavable linker[3,4]
  - Nectin-4 is a transmembrane cell adhesion molecule that is expressed in multiple tumor types, including UC[5-7]
  - Nectin-4 expression was high in nearly all patient samples tested in phase 1 and 2 EV studies
- In a phase 3 trial of EV monotherapy in previously treated patients with la/mUC, data showed improved OS versus chemotherapy, significant antitumor activity, and a tolerable safety profile[8]
- The EV + pembrolizumab (P) combination under investigation showed encouraging and durable activity (ORR 73.3%, DOR 25.6 months, and 93% of evaluable patients had reduction in target lesions), a tolerable and stable safety profile in cisplatin-ineligible patients with la/mUC in the 1L setting[9]
- FDA granted the EV+P combination Breakthrough Therapy Designation for patients with la/mUC who are cisplatin-ineligible in 1L setting[10]
- EV-302/Keynote-A39 (ClinicalTrials.gov NCT04223856) will evaluate the efficacy and safety of EV+P (Arm A) versus gemcitabine+cisplatin or carboplatin (Arm B) in 1L la/mUC

Rationale for Enfortumab Vedotin + Pembrolizumab Combination



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

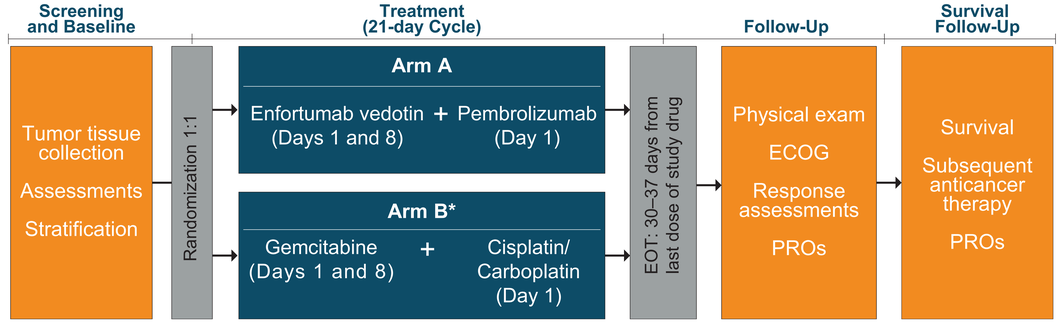


AP: Antigen-presenting cell; ATP: Adenosine triphosphate; CRT: Calreticulin; DAMPs: Damage-associated molecular patterns; ER: Endoplasmic reticulum; HMGB1: High-mobility group protein B1; ICD: Immunogenic cell death; PD-1/PD-L1: programmed cell death-ligand 1.

Preclinical studies show that ADCs linked to monomethyl auristatin E induce immunogenic cell death and may enhance anti-tumor immunity*

*Brentuximab vedotin, ladiratuzumab vedotin, and tisotumab vedotin. References: Cao et al. AACR 2016. Cao et al. Cancer Res 2017;77(13 suppl): Abstract 5588. Cao et al. Cancer Res 2018;78(13 Suppl): Abstract 2742. Alley et al. Cancer Res 2019;79(13 Suppl): Abstract 221.

EV-302/Keynote-A39 Study Design



- Primary Endpoints: OS: time from randomization to date of death (any cause); PFS: time from randomization to first documentation of disease progression per RECIST v1.1 by BICR
- Other Endpoints: ORR, DOR, DCR, AEs, PROs, PK, and biomarkers
- Stratification factors for randomization: cisplatin eligibility (eligible/ineligible), liver metastases (present/absent), PD-L1 expression (high/low)
- Follow-up until disease progression, subsequent anticancer therapy, death, consent withdrawal, or study closure

ECOG: Eastern Cooperative Oncology Group; EOT: End of Treatment; PROs: patient reported outcomes

*Maintenance therapy (after protocol specified therapy) may be used following completion and/or discontinuation of platinum-containing therapy, if locally available, and provided the patient is deemed appropriate by the investigator.

Eligibility

Key Inclusion Criteria

- ≥18 years of age with >12 weeks life expectancy
- Histologically documented, unresectable la/mUC
- Measurable disease by investigator assessment per RECIST v1.1
- 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 ≤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 EV, other vedotin ADCs, 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

Objectives and Endpoints

Primary

- OS: time from randomization to date of death (any cause); PFS: time from randomization to first documentation of disease progression per RECIST v1.1 by BICR

Secondary

- To evaluate ORR, DOR, 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 QOL and symptoms including pain from the patient perspective
- To evaluate the safety profile of each treatment regimen

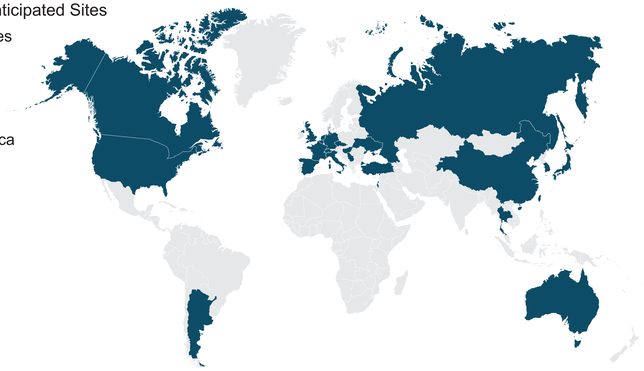
Response Assessments

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

Study Sites

Study opened in March 2020

- Active and Anticipated Sites
  - United States
  - Canada
  - Europe
  - Asia-Pacific
  - Latin-America



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Abbreviations

1L: first-line, ADC: antibody-drug conjugate, AE: adverse event, BICR: blinded independent central review, CNS: central nervous system, CT: computed tomography, DCR: disease control rate, DOR: duration of response, ECOG: Eastern Cooperative Oncology Group, ER: endoplasmic reticulum, EV: enfortumab vedotin, FDA: Food and Drug Administration, la/mUC: locally advanced/metastatic urothelial cancer, MMAE: monomethyl auristatin E, ORR: objective response rate, OS: overall survival, P: pembrolizumab, PD1: programmed cell death protein 1, PD-L1: programmed death ligand 1, PFS: progression-free survival, PRO: patient-reported outcomes, PK: pharmacokinetics, QOL: quality of life, RECIST: Response Evaluation Criteria In Solid Tumors, UC: urothelial cancer

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