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EV-202: A Phase 2 Study of Enfortumab Vedotin in Patients With Select Previously Treated Locally Advanced or Metastatic Solid Tumors

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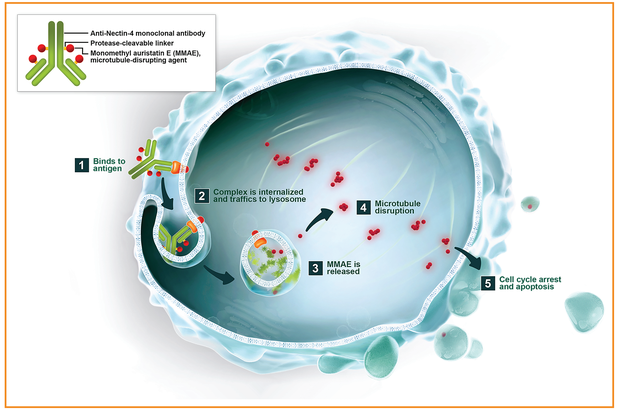
Background

- The Nectin family of cell adhesion molecules plays a role in the formation of cell-cell junctions as well as regulating many other cellular activities (eg, proliferation, survival, differentiation, polarization) in cooperation with other cell surface membrane receptors[1,2]
- Nectin-4, a transmembrane protein belonging to the Nectin family, is expressed in many solid tumors[3]
  - In normal tissue, Nectin-4 expression is moderate to weak and is mainly found in the epithelium of the bladder, skin, salivary gland ducts, gastrointestinal tract, and breast ducts[3]
- Nectin-4 is highly expressed in urothelial carcinoma (UC), and to varying degrees in breast cancer, non-small cell lung cancer, and esophageal cancers[3]
  - Nectin-4 directed therapy may add a novel treatment approach for these tumors
- Enfortumab vedotin (EV) is an antibody-drug conjugate (ADC) comprised of a fully human, monoclonal antibody directed at Nectin-4 designed to deliver monomethyl auristatin E, a microtubule disrupting agent, to cells expressing Nectin-4 leading to cell cycle arrest and cell death (Figure 1)
  - In preclinical studies, EV significantly inhibited tumor growth in Nectin-4 expressing patient-derived xenograft models of bladder, breast, and pancreatic cancer, and resulted in tumor regression in bladder and breast xenografts[3]

Figure 1. Proposed Mechanism of Action of Enfortumab Vedotin

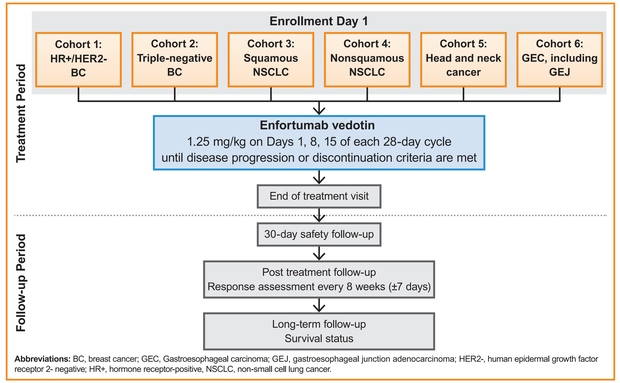


- In a phase 2 study (EV-201; NCT03219333), EV was the first ADC to demonstrate substantial clinical activity in adult patients with locally advanced or metastatic UC (la/mUC) who have previously received a programmed death receptor-1 or programmed death ligand-1 inhibitor (PD-1/L1) and a platinum-containing chemotherapy in the neoadjuvant/adjuvant locally advanced or metastatic setting[4]
  - In December 2019 EV was approved by the United States FDA under accelerated approval based on the tumor response rate observed in EV-201; continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials
- Given the broad expression of Nectin-4 across a variety of tumors, and the activity seen in patients with advanced UC, EV is being evaluated in additional advanced stage tumor types, in which microtubule disruptors have been part of the treatment paradigm, in a phase 2 study (EV-202; NCT04225117)
  - In the EV-202 study, the use of EV is investigational
- As of 15 May 2020, EV-202 is on temporary recruitment hold to alleviate the strain on global healthcare resources during the COVID-19 pandemic; please refer to clinicaltrials.gov for the current study status

Study Objective

- EV-202 will assess the antitumor activity, safety, and tolerability of 1.25 mg/kg EV in patients with previously treated locally advanced/metastatic malignant solid tumors (Figure 2)
  - The primary objective of this study is to determine the antitumor activity of EV per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by the investigator

Figure 2. EV-202 Study Design



Abbreviations: BC, breast cancer; GEC, Gastroesophageal carcinoma; GEJ, gastroesophageal junction adenocarcinoma; HER2-, human epidermal growth factor receptor 2- negative; HR+, hormone receptor-positive; NSCLC, non-small cell lung cancer.

Methods

Study Design, Treatments, and Endpoints

- This open-label, multicohort, phase 2 study was designed to assess the antitumor activity and safety of single-agent EV in adult patients with locally advanced or metastatic malignant solid tumors who have progressed on prior standard anticancer treatment (Figure 2)
  - All patients will receive EV 1.25 mg/kg administered intravenously on Days 1, 8, and 15 of each 28-day cycle until treatment discontinuation criteria are met
  - Dose reductions/interruptions will be permitted
- Approximately 240 patients with histologically or cytologically confirmed disease and an Eastern Cooperative Oncology Group (ECOG) performance score ≤1 will be enrolled into one of six tumor-specific cohorts, with approximately 40 patients each
  - For each cohort, an interim analysis is planned, based on a Bayesian optimal phase 2 design limited to two stages
  - If the number of patients with a confirmed response is less than a prespecified number of responders in stage 1, the cohort enrollment may stop; otherwise, enrollment will continue until the planned sample size is reached

Key Eligibility Criteria

- Across all cohorts, patients must be adults (according to local regulations) with histologically or cytologically confirmed locally advanced or metastatic disease, who have progressed on or after the last treatment regimen, and who have an ECOG performance score ≤1, as well as archival tumor tissue from either the primary tumor or a metastatic site; if no archival tumor tissue is available, the patients will have a mandatory biopsy to obtain tumor tissue prior to study treatment; disease-specific criteria are detailed in Table 1
  - While assessment of Nectin-4 expression is not required for enrollment, it is being tested retrospectively

A new open-label phase 2 study, EV-202, is evaluating the efficacy and safety of single-agent enfortumab vedotin in patients with previously treated locally advanced/metastatic malignant solid tumors including breast, non-small cell lung, head and neck, and gastroesophageal cancers.

Table 1. Disease-specific Inclusion Criteria

Cohort	Disease-specific Inclusion Criteria
Cohort 1: HR+/HER2- BC	• Histologically or cytologically confirmed HR+/HER2- BC not considered a candidate for further hormonal therapy ◦ Patients will be considered HR+ if biopsies show ≥1% expression of ER or PR as per current ASCO/CAP guidelines • Patient has progressed, relapsed, or discontinued for toxicity during or after receiving endocrine or hormonally directed therapy with CDK inhibitors
Cohort 2: Triple-negative BC	• Histologically or cytologically confirmed TNBC, defined as unequivocal TNBC histology (ER-negative/PR-negative/HER2-negative) ◦ Unequivocal TNBC histology: <1% expression of ER and PR by IHC, and that are, for HER2, either 0 to 1+ by IHC, or IHC 2+ and FISH-negative (not amplified) as per current ASCO/CAP guidelines • Patient received prior therapy with an anti-PD-1/L1 based on tumor PD-1/PD-L1 expression and has progressed or discontinued treatment due to toxicity, or therapy is contraindicated
Cohort 3: Squamous NSCLC	• Histologically or cytologically confirmed squamous NSCLC, where patients with mixed histology NSCLC are eligible provided there is not any component of neuroendocrine histology ◦ Patients with known *EGFR*, *ALK*, *ROS*, *BRAF*, or other actionable mutations are eligible if treated with mutation-targeted therapy and have progressed, relapsed, or discontinued treatment due to toxicity • Patient received prior therapy with an anti-PD-1/L1 based on tumor PD-1/PD-L1 expression and has progressed or discontinued treatment due to toxicity, or therapy is contraindicated
Cohort 4: Nonsquamous NSCLC	• Histologically or cytologically confirmed nonsquamous NSCLC, where patients with mixed histology NSCLC are eligible provided there is not any component of neuroendocrine histology ◦ Patients with known *EGFR*, *ALK*, *ROS*, *BRAF*, or other actionable mutations are eligible if treated with mutation-targeted therapy and have progressed, relapsed, or discontinued treatment due to toxicity • Patient received prior therapy with an anti-PD-1/L1 based on tumor PD-1/PD-L1 expression and has progressed or discontinued treatment due to toxicity, or therapy is contraindicated
Cohort 5: Head and neck cancer	• Histologically or cytologically confirmed head and neck cancer ◦ Primary tumor site must arise from the oral cavity, oropharynx, hypopharynx, and larynx; tumors arising from the nasopharynx are excluded • Patient received prior therapy with an anti-PD-1/L1 based on tumor PD-1/PD-L1 expression and has progressed or discontinued treatment due to toxicity, or therapy is contraindicated
Cohort 6: GEC, including GEJ	• Histologically or cytologically confirmed gastric, GEJ, or esophageal cancer • Subject must have received a HER2-directed therapy if known to have HER2-positive cancer

Abbreviations: ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BC, breast cancer; CDK, cyclin-dependent kinase; ER, estrogen receptor; FISH, fluorescence in situ hybridization; GEC, gastroesophageal carcinoma; GEJ, gastroesophageal junction adenocarcinoma; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; PD-1/PD-L1, programmed death receptor-1/programmed death ligand-1; PR, progesterone receptor; TNBC, triple-negative breast cancer.

Key Exclusion Criteria

- Any patient with active central nervous system metastases, grade ≥2 preexisting sensory or motor neuropathy, grade ≥3 immunotherapy-related hypothyroidism or panhypopituitarism, ongoing grade >3 immunotherapy-related adverse events (AEs) requiring high-dose steroids, or a history of uncontrolled diabetes mellitus within 3 months of the study, will be excluded

Endpoints

- The primary endpoint of this study is confirmed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by the investigator
- Secondary efficacy endpoints include progression-free survival (PFS), duration of response (DoR), and disease control rate (DCR) per investigator assessment, and overall survival (OS)
- Safety and tolerability variables are additional secondary endpoints

Assessments and Statistical Analyses

- Radiological assessments of tumor response status will be performed at baseline and every 8 weeks then reduced to every 12 weeks after 1 year
  - Complete response (CR) or partial response (PR) will be confirmed 4 weeks after after the first response
- Confirmed ORR and DCR for each cohort will be calculated and its 95% confidence interval (CI) will be constructed by the Clopper-Pearson method
- Time-to-event endpoints (eg, DoR, PFS, and OS) will be analyzed using Kaplan-Meier methodology; data will be provided as median and the corresponding 2-sided 95% CI
- The tolerability and safety of EV will be assessed by monitoring AEs, including adverse drug reactions and toxicities, as well as changes in vital sign measurements, laboratory assessments, and 12-lead ECG

Additional EV Studies

- Enfortumab vedotin is actively being evaluated in patients with la/mUC in other studies
  - **EV-101 (NCT02091999):** Phase 1 dose-escalation/-expansion study of single-agent EV
  - **EV-103 (NCT03288545):** Phase 1/2 study of EV as a single agent or combined with an immune checkpoint inhibitor and/or chemotherapy in patients with la/mUC or muscle-invasive bladder cancer
  - **EV-201 (NCT03219333):** Pivotal phase 2 study in which patients must have progression on anti-PD-1/L1 therapy and prior treatment with platinum-containing chemotherapy (cohort closed) or have progressed on anti PD-1/L1 therapy and are platinum-naïve and ineligible for cisplatin treatment (cohort enrolling)
  - **EV-301 (NCT03474107):** Confirmatory phase 3 trial of EV versus investigator-determined chemotherapy (docetaxel, paclitaxel, or vinflunine) in patients who have received one prior platinum-containing chemotherapy, and have experienced disease progression during or following treatment with a PD-1/L1 treatment
  - **EV-302 (NCT04223856):** Phase 3 study of EV plus pembrolizumab, with or without chemotherapy, compared with chemotherapy alone in patients with untreated la/mUC
  - **MORPHEUS-MUC (NCT03869190):** Phase 1b/2 umbrella study of multiple immunotherapy-based treatment combination, which includes a cohort combining atezolizumab plus EV

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Please direct any questions or comments regarding this poster to Biplob Dass, PhD (Biplob.Dass@astellas.com).