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EV-202: Phase 2 Trial-in-Progress of Enfortumab Vedotin for Previously Treated Advanced Solid Tumors, Including Breast Cancer

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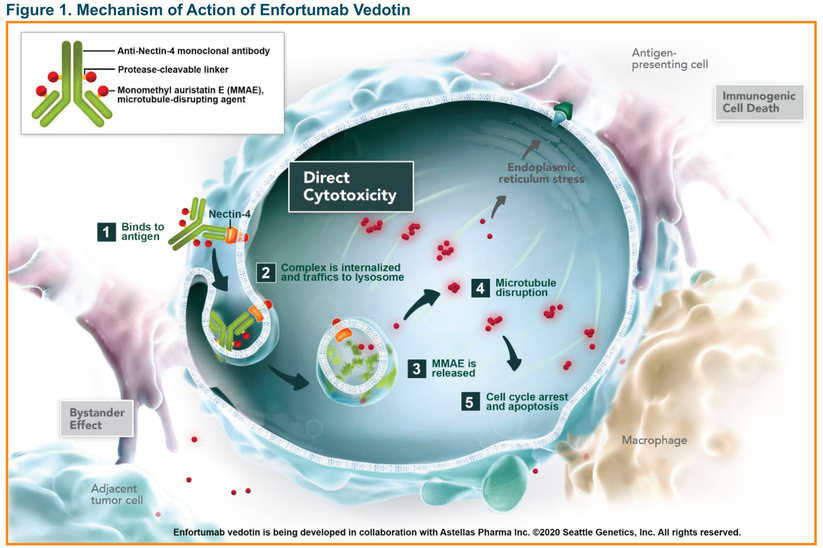
Background

- Despite therapy advances, breast cancer is anticipated to be the second leading cause of cancer death among women in the United States (US) in 2021[1]
  - The 5-year survival rate for metastatic breast cancer is about 28%[1,2]
- Hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer accounts for up to ~73% of US breast cancer cases with known HR/HER2 status, yet factors contributing to worse overall survival include number of metastatic sites, sites of metastases, type of prior therapy received, and response to prior therapy[3-5]
- Although less common, triple-negative breast cancers have an aggressive clinical course, poor prognosis, and are generally managed with chemotherapy, despite potentially worse outcomes; the lack of effective treatments represents a critical unmet need[6-8]
- Nectin-4, a cell adhesion molecule, is detected at strong or moderate staining intensity by immunohistochemistry in ~53% of breast cancer specimens; therefore, Nectin-4–directed therapies represent a novel approach in breast cancer[9]
- Enfortumab vedotin (EV) is an antibody-drug conjugate comprised of a fully human monoclonal antibody directed against Nectin-4, and monomethyl auristatin E (MMAE), a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker[10]
  - MMAE release within the cell disrupts the microtubule network, inducing cell cycle arrest and apoptosis (Figure 1)

Figure 1. Mechanism of Action of Enfortumab Vedotin



- In EV-301, a phase 3 trial of patients with previously treated locally advanced or metastatic (la/m) urothelial carcinoma, EV significantly prolonged overall survival (OS) versus chemotherapy (docetaxel, paclitaxel, vinflunine)[11]
- EV is approved by the US Food and Drug Administration for the treatment of adults with la/m urothelial carcinoma who have previously received a programmed cell death protein-1/programmed death-ligand 1 (PD-1/L1) inhibitor and platinum-based chemotherapy, or are ineligible for cisplatin-containing chemotherapy and have previously received one or more lines of therapy[10]; EV is also approved by Japan's Ministry of Health, Labour, and Welfare for radically unresectable urothelial carcinoma that has progressed after anticancer chemotherapy and is under review by the European Medicines Agency for urothelial carcinoma[12,13]

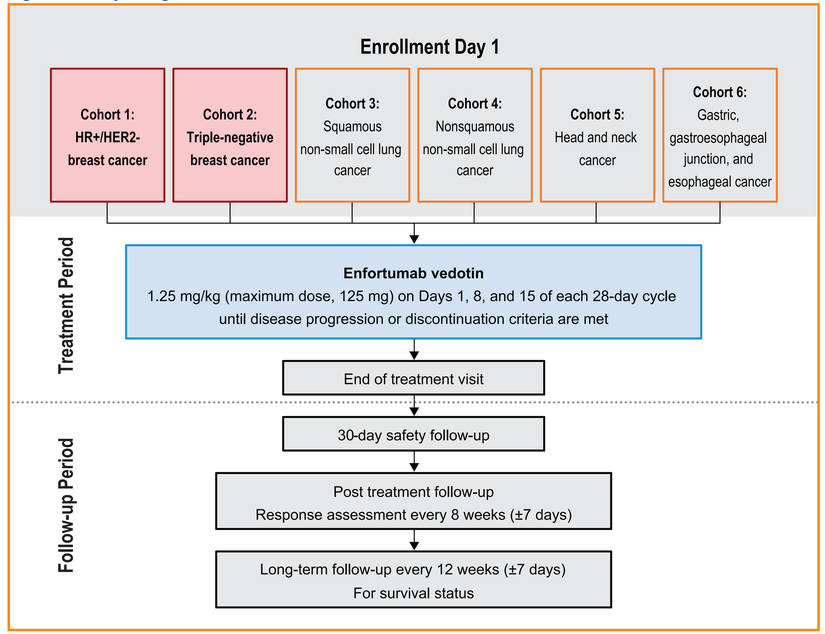
Aim/Objective

- EV-202 (NCT04225117) aims to evaluate the efficacy and safety/tolerability of EV in patients with previously treated la/m malignant solid tumors

Methods

- EV-202 is a multicenter, multicohort, open-label phase 2 study
- About 240 patients (~40 patients/cohort) with histologically/cytologically confirmed disease and Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 are enrolling into six tumor-specific cohorts, including two breast cancer cohorts (Figure 2)

Figure 2. Study Design



Abbreviations: HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive.

Key Eligibility Criteria

- Inclusion
  - ECOG performance status score ≤1
  - Archival tumor tissue from either the primary tumor or metastatic site
  - Within the HR+/HER2- breast cancer cohort, patients must have progressed, relapsed, or discontinued therapy for toxicity after one (no more than two) cytotoxic regimen (taxane/anthracycline) for incurable, la/m disease
    - No limit applies to endocrine therapies
    - Prior cytotoxic regimen in the neoadjuvant/adjuvant setting counts as prior cytotoxic regimen if disease recurrence occurred within 6 months of regimen completion
    - Patients must have progressed, relapsed, or discontinued for toxicity after endocrine/hormonally directed therapy with cyclin-dependent kinase inhibitors
  - Within the triple-negative breast cancer cohort, patients must have progressed, relapsed, or discontinued therapy for toxicity after one (no more than two) cytotoxic regimen (taxane/anthracycline) for incurable, la/m disease
    - Prior cytotoxic regimen in the neoadjuvant/adjuvant setting counts as prior cytotoxic regimen if disease recurrence occurred within 6 months of regimen completion
    - Patients must have progressed/discontinued for toxicity after prior PD-1/L1 inhibitor therapy, if eligible
- Exclusion
  - Active central nervous system metastases
  - Grade ≥2 sensory/motor neuropathy
  - Ongoing grade ≥3 immunotherapy-related hypothyroidism/panhypopituitarism
  - Ongoing immunotherapy-related adverse events requiring high-dose steroids
  - Uncontrolled diabetes mellitus
- Nectin-4 expression is not required for eligibility and is being tested for exploratory outcomes

Endpoints

- The primary endpoint is investigator-assessed confirmed objective response rate (ORR) (per RECIST v1.1)
- Secondary efficacy endpoints (per investigator-assessed RECIST v1.1) are:
  - Duration of response (DoR)
  - Disease control rate (DCR)
  - Progression-free survival (PFS)
  - OS
- Safety/tolerability is a secondary safety endpoint

Assessments

- Disease assessments every 8 weeks (±7 days) and then every 12 weeks (±7 days) after 1 year of treatment
- Safety/tolerability evaluation by monitoring adverse events and assessments via laboratory tests, vital signs, physical examination, and electrocardiogram
- Complete eye examination at screening and as clinically indicated

Statistical Analyses

- An interim analysis for futility is planned for each cohort
- All patients receiving ≥1 EV dose, with measurable disease at baseline, and with either two postbaseline tumor assessments or not in the follow-up of response at the time of analysis will be included in the efficacy analysis
- Confirmed ORR and DCR will be analyzed with the Clopper-Pearson method for each tumor type
- DoR, PFS, and OS will be analyzed with the Kaplan-Meier method

An open-label phase 2 study, EV-202, is evaluating the safety and efficacy of EV in patients with previously treated la/m malignant solid tumors, including breast cancer

Study Status

- Recruitment is ongoing at approximately 50 sites in North America and Japan
- The target enrollment is 240 patients
- Additional trial detail can be found at: https://clinicaltrials.gov/ct2/show/NCT04225117

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